The American Journal of Medicine

INDEX NUMBER

June 1953

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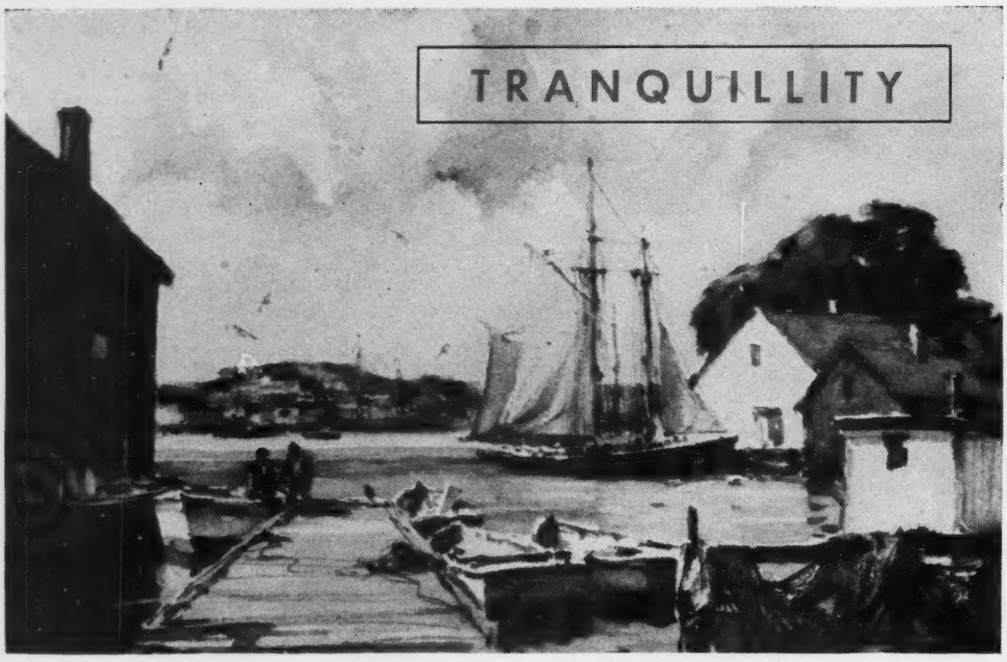

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Editorial

Anticoagulant Therapy in Acute Myocardial Infarction
HENRY I. RUSSEK AND BURTON I. ZOHMAN 651

Clinical Studies

Effect of Weight Reduction and Caloric Balance on Serum Lipoprotein and Cholesterol Levels
LT. COL. WELDON J. WALKER, ELEANOR Y. LAWRY, DONALD E. LOVE, GEORGE V. MANN, SAMUEL A. LEVINE AND FREDERICK J. STARE 654

This carefully controlled and conservatively analyzed study provides objective data on a subject concerning which there has been much wishful thinking and loose talk: the effect of weight reduction induced by caloric restriction, on the serum levels of lipids and lipoproteins, presumptive agents in the causation of atherosclerosis. The results leave little doubt that caloric restriction does lead to significant reduction of these serum components, particularly if the initial concentration of Sf 12-20 lipoprotein exceeds 50 mg. per cent. Of interest is the fact that a generous cholesterol intake (two eggs daily) makes no significant difference in the results.

Hypercholesterolemia, Myxedema and Atherosclerosis
HERRMAN L. BLUMGART, A. STONE FREEDBERG AND GEORGE S. KURLAND 665

On the basis of negative autopsy findings in eight cases of myxedema surgically induced for intractable heart failure, the authors make the point that atherosclerotic coronary artery disease is not a necessary or indeed a common consequence of myxedema, a view supported also by the findings in spontaneous myxedema in adults and to some extent in cretinism. It should be noted that in four of the eight cases cited, all treated with small doses of thyroid, the serum cholesterol levels, though significantly higher than preoperatively, were nevertheless not excessive.

Failure of Ingestion of Cream to Affect Blood Coagulation
JOHN A. TULLOCH, RALPH S. OVERMAN AND IRVING S. WRIGHT 674

It has been claimed that ingestion of fat is followed by acceleration of blood clotting. The present authors show convincingly that this alleged effect is due to an artefact, the presence of thrombin on the surface of reused glass syringes. If the blood clotting time is measured before and after ingestion of cream, using proper precautions, no significant change occurs.

An Evaluation of Anticoagulant Therapy in Myocardial Infarction Based on Prognostic Categories
ROBERT H. FURMAN, CON O. T. BALL, ROBERT G. GALE, F. TREMAINE BILLINGS, JR. AND GEORGE R. MENEELY 681

In "very poor risk" patients with myocardial infarction, prognosis was found to be exceedingly poor and anticoagulants did not help; in "good risk" patients with myocardial infarction, prog-

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The American Journal of Medicine

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nosis is so good anyway that anticoagulants do not make any perceptible difference. It is in the "poor risk" patients (myocardial infarction with shock, congestive failure, diabetes or azotemia) that anticoagulants are found to decrease mortality unequivocally, and it is probably only in this category that anticoagulant therapy is uniformly indicated.

Control of Prothrombin Activity with Tromexan Therapy
MURRAY WEINER, GEORGE SIMSON, J. J. BURNS, J. MURRAY STEELE AND BERNARD B. BRODIE 689

Having developed chemical methods for the estimation of tromexan in body fluids so as to determine its rate of absorption, degradation and excretion, the authors go on in this study to correlate this information with effects on prothrombin activity. As with all anticoagulants, there is considerable diversity in the degree of early and sustained response to tromexan in different patients so that establishment of one generally effective dosage regimen is difficult. Tromexan appears to be more uncertain than dicumarol in this regard.

Clinical Evaluation of Ethyl Biscoumacetate (Tromexan)
JOSEPH B. VANDER VEER, ELMER H. FUNK, JR., FRANK R. BOYER, AND ERNEST A. KELLER 694

In this evaluation in 116 patients of the usefulness of the anticoagulant ethyl biscoumacetate (Tromexan), it was found that the drug exerted its effects more quickly than dicumarol but that regulation was more difficult. Tromexan may have a place in short term and prophylactic anticoagulant therapy but does not appear to be well suited to regular long-term use.

Clinical Use of a New Anticoagulant, Phenylindanedione. Report of 400 Cases
ANCEL BLAUSTEIN, NED SHNAYERSON AND ROBERT WALLACH 704

Despite the paucity of details, this report on the use of phenylindanedione in 400 cases indicates that it may prove to be a welcome addition to the roster of anticoagulants. Its action is rapid, it is not cumulative, regulation of dosage appears to be comparatively easy, resistance is uncommon and uncontrolled hemorrhage is infrequent.

Review

Serum Cholinesterase in Health and Disease LOUIS J. VORHAUS AND ROBERT M. KARK 707

This presentation, chiefly a composite study of the authors' results with the Michel electrometric method, gives an over-all picture of the effects of various diseases and drugs on serum cholinesterase levels. The authors believe the determination to be of special value as an indication of the degree of liver cell damage in hepatitis. A number of interesting points are made including an estimate of twenty-eight days for the life span of the serum cholinesterase molecule.

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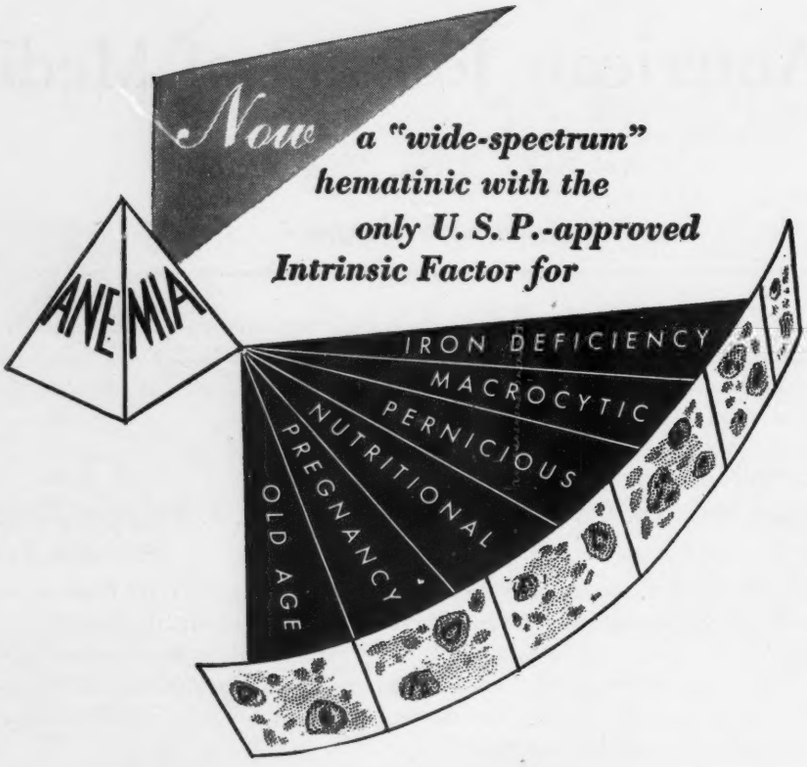

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Seminars on Blood Coagulation

An Evaluation of Anticoagulant Therapy. . . . . IRVING S. WRIGHT 720

Dr. Wright here effectively and concisely puts together the case for anticoagulant therapy with special reference to myocardial infarction. He also reviews the properties, advantages and disadvantages of the several anticoagulants presently available: dicumarol, heparin, tromexan, cyclocumarol, phenylindanedione, paritol, treburon, crystalline trypsin. This authoritative survey offers excellent orientation in this controversial field and is up-to-date.

Clinic on Psychosomatic Problems

Anaclitic Treatment in a Patient with Ulcerative Colitis 731

Clinic on Psychosomatic Problems (Massachusetts General Hospital)—

In a subject afflicted with ulcerative colitis and presenting an exceedingly complex "schizoaffective psychotic reaction," a long, patient program of treatment embodying the principles of anaclitic therapy was instituted, with favorable response. The description of patient and management is of unusual interest.

Clinico-pathologic Conference

Progressive Central Nervous System Disease 736

Clinico-pathologic Conference (Washington University School of Medicine)—

This patient, in addition to presenting many of the common afflictions of old age, offered an intriguing problem in interpretation of neurologic findings which could be resolved completely only at necropsy. The discussion is lively and informative.

Research Society Abstracts

The Southern Society for Clinical Research—Abstracts of Papers Presented at the Seventh Annual Meeting, New Orleans, Louisiana, January 31, 1953 . . . 745

Case Reports

Chronic Keratoderma Blenorrhagica with Ankylosing Polyarthritis Deformans. Report of a Case with Autopsy Findings S. P. STUBBS, W. C. CORWIN AND E. B. HANAN 763

This syndrome is not well known to internists and this case report will be found of interest.

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Thyroid Carcinoma. Visualization of a Distant Osseous Metastasis by Scintiscanner; Observations during I-131 Therapy

NORMAN W. SPECHT, FRANZ K. BAUER AND RALPH M. ADAMS 766

This report illustrates the application of a new refinement in counting technics, the gamma detecting directional scintillation counter, to problems in visualization and treatment of thyroid carcinoma and metastases. Among other interesting points brought out is the close correspondence between the outline of the scintigram and the shape of the metastatic mass found at necropsy.

Traumatic Chylothorax

A. M. Sabety, John J. Thompson and Harry Halprin 770

An interesting discussion of chylohorax, including use of a lipophilic dye to establish the diagnosis of ruptured thoracic duct.

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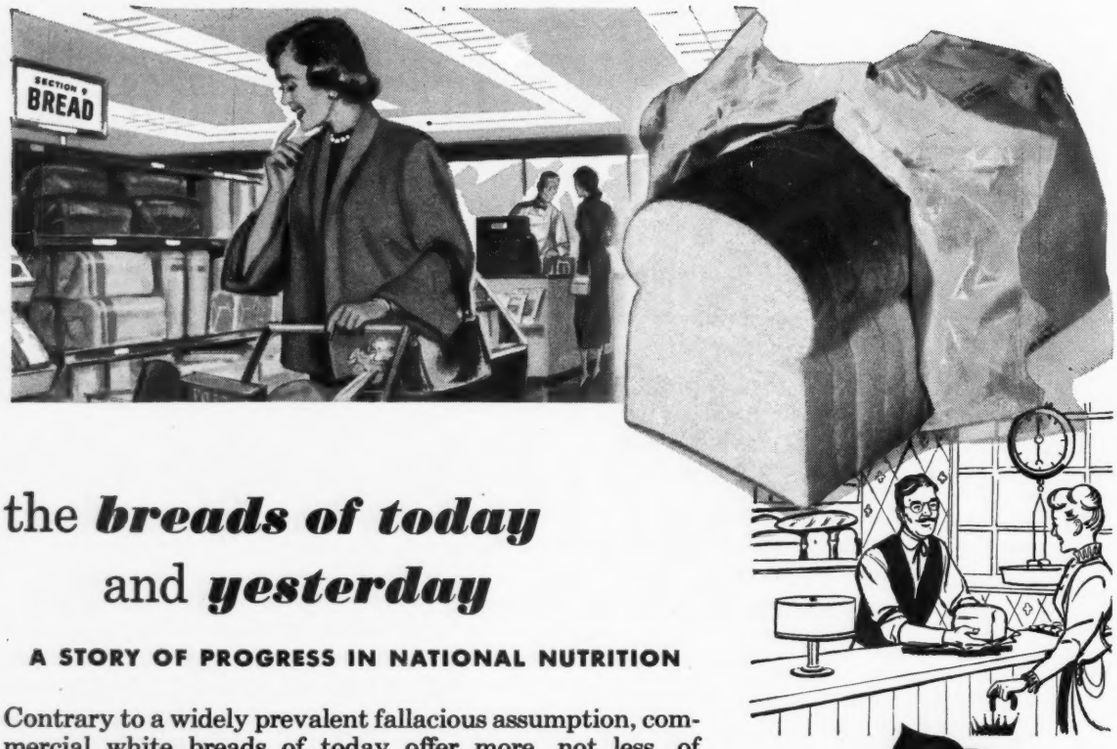

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1. Flour and Bread Enrichment, 1949-50: Prepared by The Committee on Cereals, Food and Nutrition Board, National Research Council, Washington, D.C., 1950.

2. Geddes, W.F.: Cereal Chemists Guard Nutrition, Agricultural and Food Chemistry *1*:38 (Apr.) 1953.

3. Bakery Products; Definitions and Standards of Identity, Federal Register *17*:4453 (May 15) 1952.

4. Sherman, H.C.: Chemistry of Food and Nutrition, ed. 8, New York, the Macmillan Company, 1952, p. 599.

5. Goddard, V.R., and Marshall, M.W.: The Calcium Content of Commercial White Bread, United States Department of Agriculture, Technical Bull. No. 1055, 1952.

Crespo, S., and Bradley, W.B.: Calcium and Milk Content of Commercial White Bread. Report by the Laboratories of the American Institute of Baking, Feb. 28, 1950.

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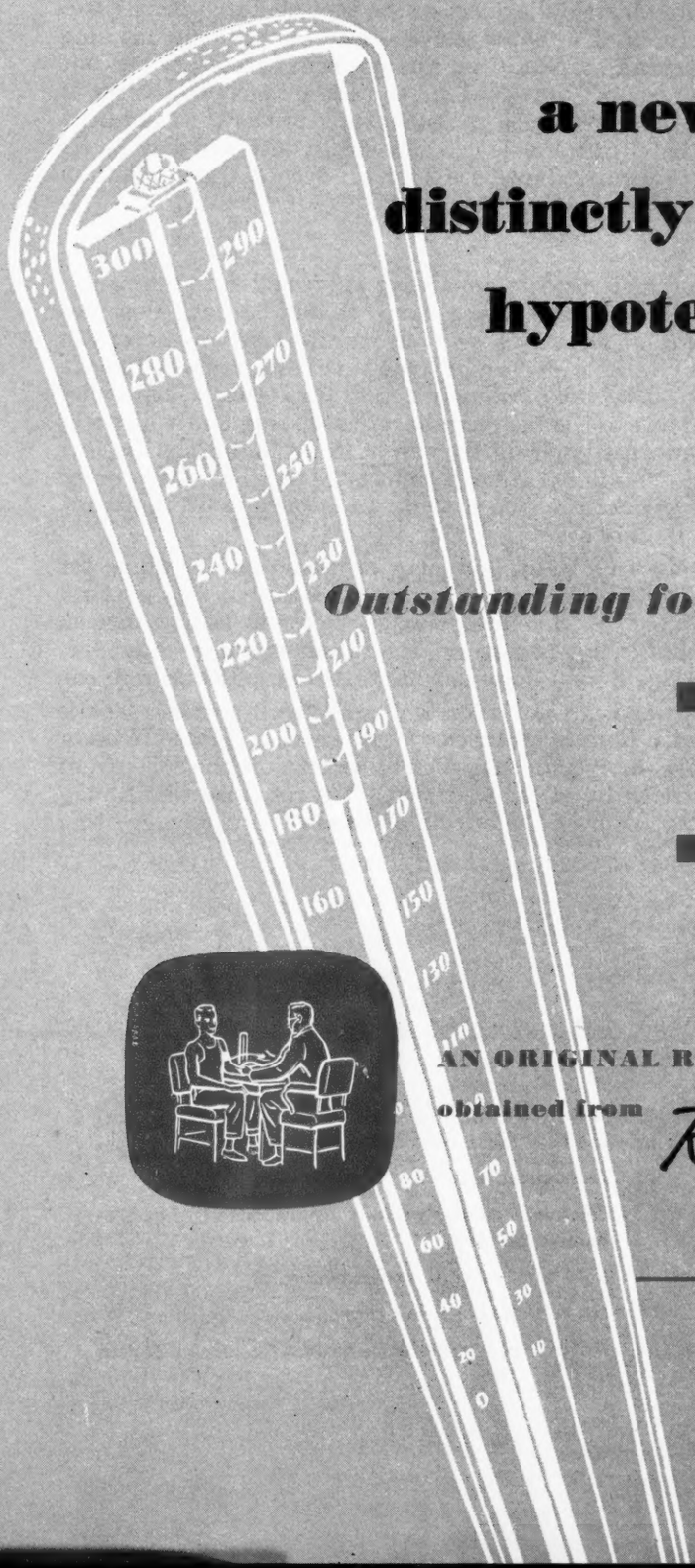

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References:

1. Wilkins, R.W., and Judson, W.E.: The Use of Rauwolfia Serpentina in Hypertensive Patients, New England J. Med. *248*:48 (Jan. 8) 1953.

2. Wilkins, R.W.; Judson, W.E., and Stanton, J.R.: Preliminary Observations on Rauwolfia Serpentina in Hypertensive Patients, Proc. New England Cardiovas. Soc., 1951-1952, p. 34.

3. Vakil, R.J.: A Clinical Trial of Rauwolfia Serpentina in Essential Hypertension, Brit. Heart J. *11*:350 (Oct.) 1949.

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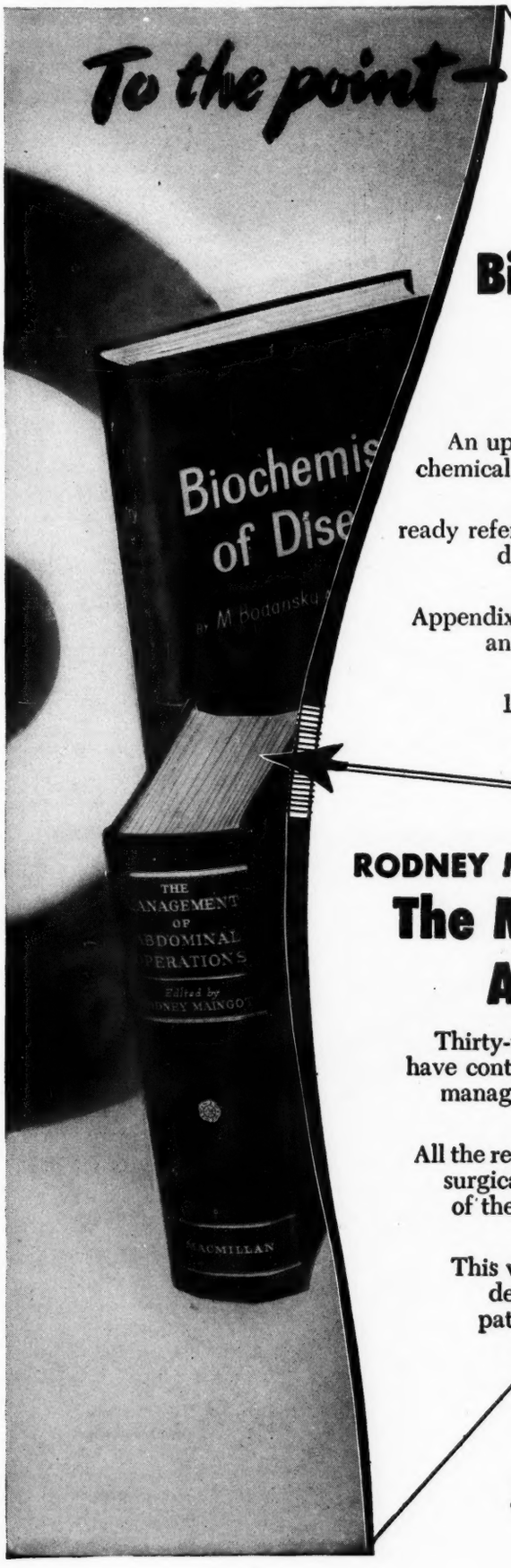

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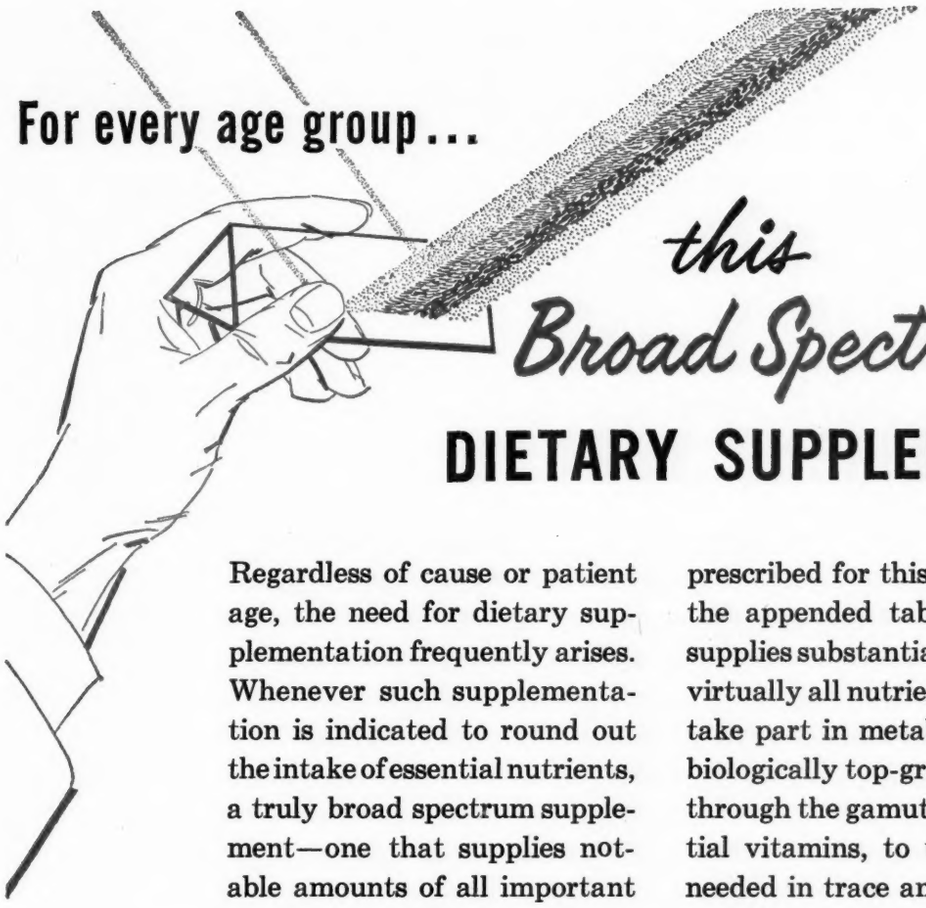

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(Each serving made of ½ oz. of Ovaltine and 8 fl. oz. of whole milk)

MINERALS		VITAMINS	
*CALCIUM	1.12 Gm.	*ASCORBIC ACID	37 mg.
CHLORINE	900 mg.	BIOTIN	0.03 mg.
COBALT	0.006 mg.	CHOLINE	200 mg.
*COPPER	0.7 mg.	FOLIC ACID	0.05 mg.
FLUORINE	3.0 mg.	*NIACIN	6.7 mg.
*IODINE	0.15 mg.	PANTOTHENIC ACID	3.0 mg.
*IRON	12 mg.	PYRIDOXINE	0.6 mg.
MAGNESIUM	120 mg.	*RIBOFLAVIN	2.0 mg.
MANGANESE	0.4 mg.	*THIAMINE	1.2 mg.
*PHOSPHORUS	940 mg.	*VITAMIN A	3200 I.U.
POTASSIUM	1300 mg.	VITAMIN B_{12}	0.005 mg.
SODIUM	560 mg.	*VITAMIN D	420 I.U.
ZINC	2.6 mg.		

*PROTEIN (biologically complete) . . . . . 32 Gm.
*CARBOHYDRATE . . . . . 65 Gm.
*LIPIDS . . . . . 30 Gm.

*Nutrients for which daily dietary allowances are recommended by the National Research Council

when nutritional reinforcement is necessary...

Today, the concept of interrelationship in nutrition is widely recognized. For this reason, when special restrictive diets are prescribed, the physician will usually tend to supplement dietary intake with the most complete vitamin-mineral formulation available. "Clusivol" is an ideal preparation for such therapy.

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2 "Clusivol" Capsules (average daily dosage) provide:

Vitamin A (synthetic)	25,000	U.S.P. Units
Vitamin D (irradiated ergosterol)	2,000	U.S.P. Units
Vitamin C (ascorbic acid)	150.0	mg.
Thiamine HCl (B_1)	10.0	mg.
Riboflavin (B_2)	5.0	mg.
Pyridoxine HCl (B_6)	1.0	mg.
Panthenol, equivalent to of calcium pantothenate	10.0	mg.
Vitamin B_{12} U.S.P. (crystalline)	2.0	mcg.
Folic acid	2.0	mg.
Nicotinamide	100.0	mg.
Vitamin E (as mixed tocopherols natural)	10.0	mg.
Inositol	30.0	mg.
Choline—from choline bitartrate	30.0	mg.
Biotin	0.1	mg.
d-Methionine	20.0	mg.
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Copper—from copper sulfate	1.0	mg.
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Iron—from 4 gr. ferrous sulfate exsic.	76.2	mg.
Calcium—from dicalcium phosphate	165.0	mg.
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Iodine—from potassium iodide	0.15	mg.
Molybdenum—from sodium molybdate	0.2	mg.
Potassium—from potassium sulfate	5.0	mg.
Zinc—from zinc sulfate	1.2	mg.
Magnesium—from magnesium sulfate	6.0	mg.
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1-cc. ampoules of 5 mg. (50,000 I.U.)

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Obedrin offers a practicable solution to the problem of keeping an obese patient on a restricted diet.

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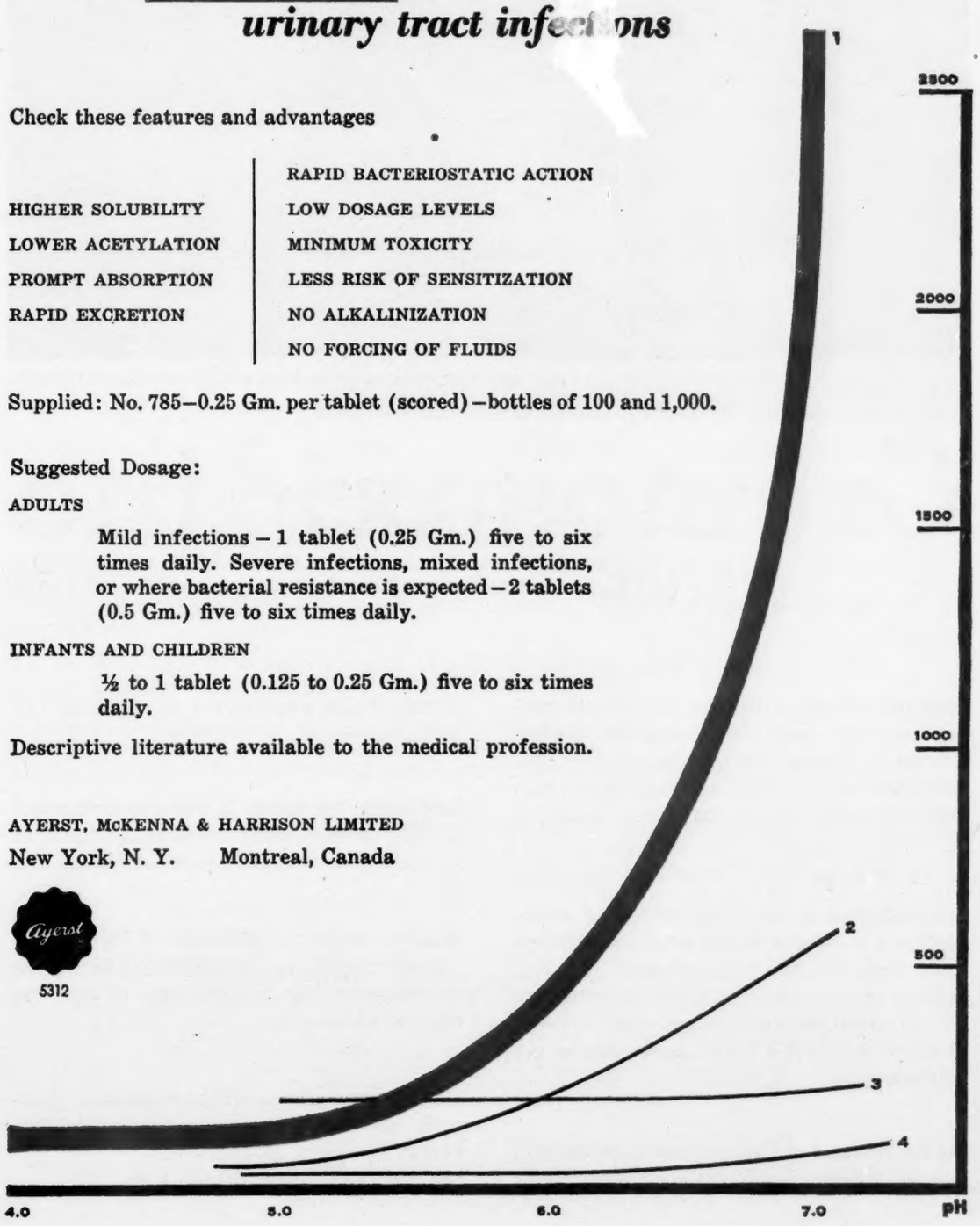

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Since the etiology of diarrhea is frequently complex, no single agent may be expected to effect prompt or complete relief. CREMOSUXIDINE contains three antidiarrhetic agents, each of which acts specifically against the several causes of diarrhea.

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As incorporated in CREMOSUXIDINE, pectin (1%) specifically helps neutralize the diarrhetic effects of many toxins and irritants, aids formation of normal stools.

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Specifically, the kaolin in CREMOSUXIDINE (1.5 Gm. per tablespoonful) acts as an adsorbent, to remove irritants, and toxic bacterial by-products.

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Because of the completeness of its formula, CREMOSUXIDINE may be relied upon to provide symptomatic relief in most types of diarrhea, regardless of etiology.

SUPPLIED

CREMOSUXIDINE, a smooth, homogeneous, pleasantly flavored suspension, is supplied in SPASAVER® bottles of 16 fluidounces.

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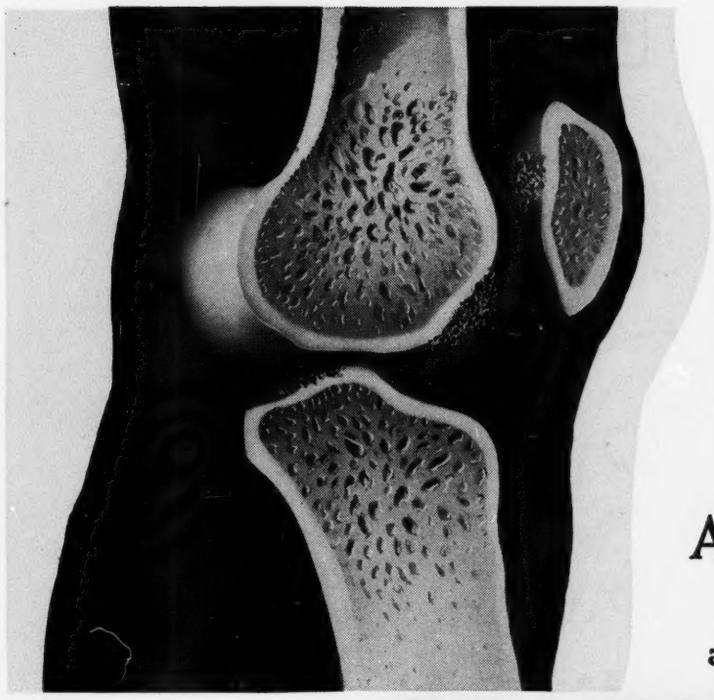

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BUTAZOLIDIN® (brand of phenylbutazone) is available as coated tablets of 200 mg. and 100 mg.

A selection from the bibliography on BUTAZOLIDIN... (1) Freyberg, R.; Kidd, E. C., and Boyce, K. C.: Studies of Butazolidin and Butapyrin in Patients with Rheumatic Diseases, Paper read before the Annual Meeting of the American Rheumatism Association, Chicago, June 6, 1952. (2) Kuzell, W. C., and others: Phenylbutazone (Butazolidin) in Rheumatoid Arthritis and Gout, J.A.M.A. *149*:729, 1952. (3) Kuzell, W. C., and Schaffarzick, R. W.: Butapyrin in Gout, Stanford M. Bull. *9*:194, 1951. (4) Kuzell, W. C., and Schaffarzick, R. W.: Phenylbutazone (Butazolidin), Bull. Rheumat. Dis. *3*:23, 1952. (5) Kuzell, W. C., and Schaffarzick, R. W.: Phenylbutazone (Butazolidin) and Butapyrin in Arthritis and Gout, California Med. *77*:319, 1952. (6) Smith, C. H., and Kunz, H. G.: Butazolidin in Rheumatoid Disorders, J. M. Soc. New Jersey *49*:306, 1952. (7) Steinbrocker, O., and others: Phenylbutazone Therapy of Arthritis and Other Painful Musculoskeletal Disorders, J.A.M.A. *150*:1087, 1952. (8) Stephens, C. A. L., Jr., and others: Benefits and Toxicity of Phenylbutazone (Butazolidin)® in Rheumatoid Arthritis, J.A.M.A. *150*:1084, 1952.

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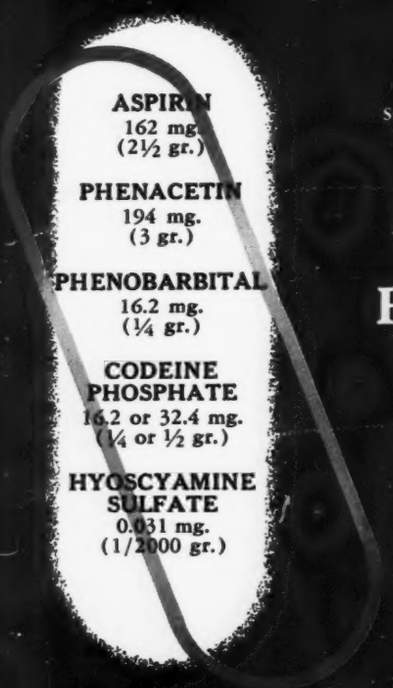

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1. **Sulfadiazine**.....0.167 Gm.
2. **Sulfamerazine**.....0.167 Gm.
3. **Sulfamethazine**.....0.056 Gm.
4. **Sulfacetamide**.....0.111 Gm.

Each tablet or teaspoonful (5 cc.) of suspension provides 0.5 Gm. of total sulfonamides.

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References: 1. Lehr, D.: Brit. M. J. 2:543-548, 1948. 2. Lehr, D.: Brit. M. J. 2:601, 1950. 3. Hawking, F., and Lawrence, J. S.: The Sulfonamides, New York, Grune and Stratton, 1951.

Deltamide—A Quadruple Sulfonamide Tablet and Suspension—represents the latest development in multiple sulfonamide therapy. Deltamide utilizes the fact that an increase in the number of sulfonamides in sulfonamide mixtures provides the significant advantages of greater clinical safety with lowered incidence of toxic and allergic reactions.[1,2]

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By combining four of the most useful sulfonamides,[3] Deltamide is superior on four counts:

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. . . you may free her from iron-deficiency anemia by the simple expedient of prescribing one IBEROL tablet t.i.d.

As you can see by the formula, three IBEROL tablets provide a therapeutic dose of iron plus seven B complex factors including B_{12}. In addition, IBEROL supplies standardized stomach-liver digest and ascorbic acid.

Compressed, triple-coated IBEROL tablets are easy to take with no trace of liver odor or taste. The outer sugar-coating masks the iron, gives the tablet a pleasant odor and flavor.

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THREE IBEROL TABLETS: the daily therapeutic dose for adults, supply:

Ferrous Sulfate, U.S.P.	1.05 Gm.
(representing 210 mg. elemental iron, the active ingredient for the increase of hemoglobin in the treatment of iron-deficiency anemia)	
Plus these nutritional constituents:	
Thiamine Mononitrate (6 times MDR*)	6 mg.
Riboflavin (3 times MDR*)	6 mg.
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Ascorbic Acid (5 times MDR*)	150 mg.
Pyridoxine Hydrochloride	3 mg.
Pantothenic Acid	6 mg.
Vitamin B_{12}	30 mcg.
Folic Acid	3.6 mg.
Stomach-Liver Digest	1.5 Gm.

*MDR—Minimum Daily Requirement
†RDA—Recommended Daily Dietary Allowance

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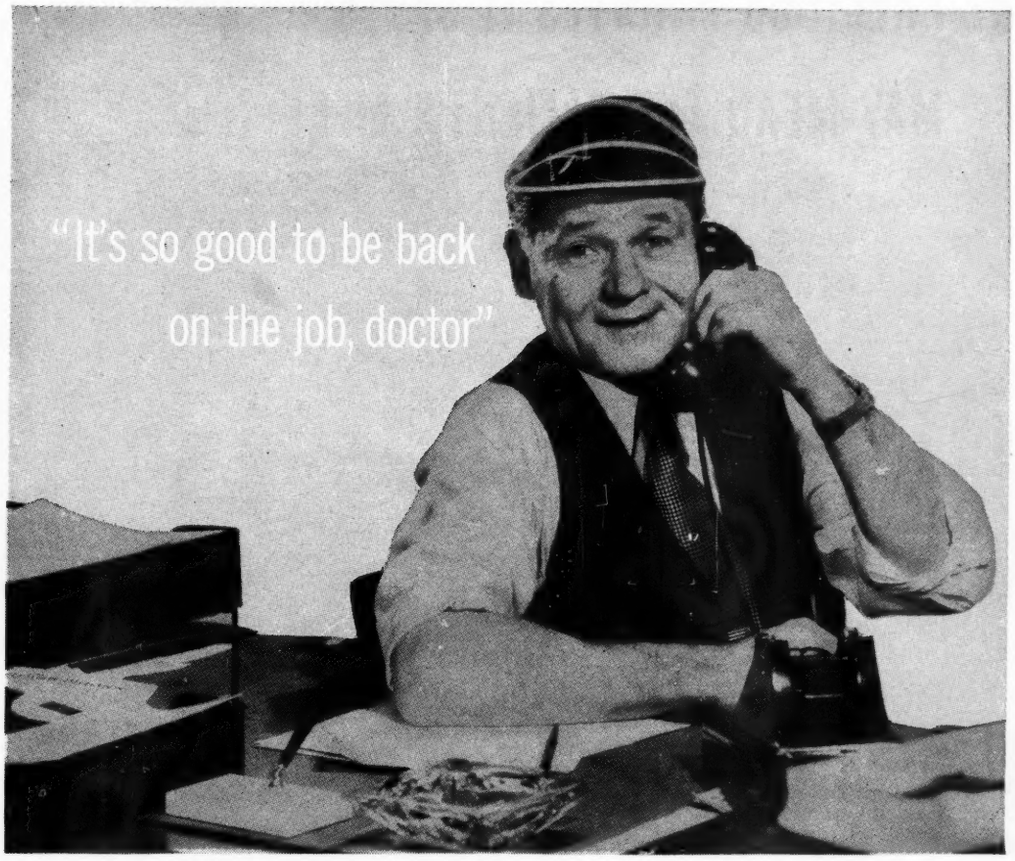

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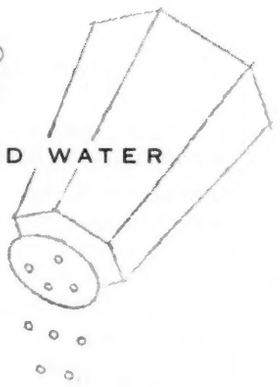

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MAY MEAN THE PATIENT'S LIFE

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(DEXTRAN) INJECTION 6%

AN EFFICIENT PLASMA VOLUME EXPANDER

Expandex can be infused intravenously at a moment's notice at the very scene of an accident because it is liquid, sterile, compatible with all blood groups, and ready for instant use. Through its desirable osmotic behavior, it expands the effective plasma volume, quickly bolstering the blood pressure and overcoming shock. Thus the precious minutes it saves, even in the face of hemorrhage, may prevent fatal circulatory failure.

In the operating room, Expandex finds equally valuable application in the treatment of shock due to hemorrhage, burns, trauma and surgery.

Expandex is sterile, nonpyrogenic, notably non-allergenic and nonantigenic, and is not stored in significant amounts in the body. It does not carry, therefore cannot transmit, the virus of hepatitis.

Injection Expandex, the first clinically acceptable dextran produced in the United States, is supplied in 500 cc. bottles, with or without a Sterile Administration Set. Available through regular sources of supply.

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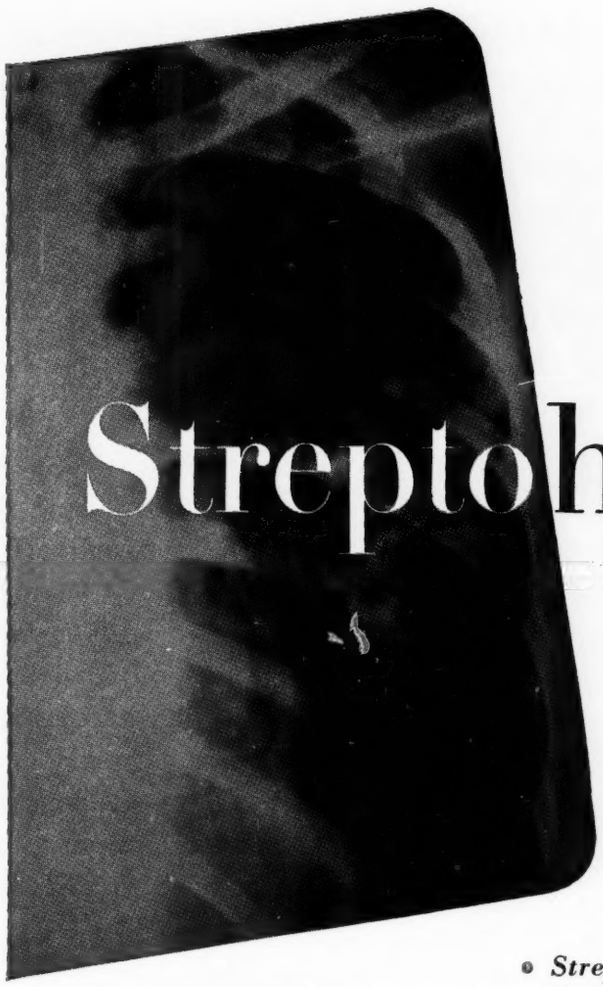

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a new crystalline compound of the two preferred antimicrobials for treatment of tuberculosis

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- ***Streptomycin produces minimal incidence of hearing loss over extended treatment periods.***
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The danger of hemorrhage, a calculated risk in anticoagulant therapy, makes the degree of cumulation of an anticoagulant the most important safety factor. Extensive clinical experience with HEDULIN (brand of phenindione or 2-phenyl-1, 3-indandione), a new anticoagulant unrelated to the coumarins, has shown this drug to be free from cumulative effects, safer, and more rapidly effective in clinical use.[1-6]

Blaustein et al.[1] report that phenindione produces a prothrombopenia more rapidly than dicumarol* and also permits prothrombin levels to return to normal more quickly. The action of phenindione is relatively uniform and less prolonged than that of dicumarol, without its cumulative effect.[4] There is minimal tendency to hemorrhage with HEDULIN: in HEDULIN-treated cases reported by Blaustein et al.,[6] the incidence of hemorrhage was only 0.75 percent.

The need for daily prothrombin time determinations is reduced. Once maintenance dosage has been established the interval between readings may be as long as 7 to 14 days. Clinical evidence suggests the use of HEDULIN in coronary thrombosis and myocardial infarction; aortic thrombosis; postpartum thrombosis and thrombophlebitis, selected cases of congestive heart failure; pulmonary embolism, aneurysm, and infarction; cerebral thrombosis; and in the prophylaxis of postpartum and postoperative thromboembolic disorders.

References:

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5. Preston, F. W., et al.: Circulation VI: 515, 1952.
6. Blaustein, A. U., et al.: Am. J. Med. To be published.

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NEW... council-accepted
oral anticoagulant
(not a coumarin derivative)
with a wide range of safety

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Permits dependable prothrombin control with little risk of dangerous fluctuations

- **HEDULIN is not cumulative in effect—provides greater uniformity of action and ease of maintenance**
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- **HEDULIN acts promptly, producing therapeutic prothrombin levels in 18-24 hours**
- **HEDULIN requires fewer prothrombin determinations—only one in 7 to 14 days, after maintenance dose is established**
- **HEDULIN's anticoagulant action is rapidly reversed by vitamin K_1 emulsion**

DOSAGE: 4 to 6 tablets (200 to 300 mg.) initially, half in the morning and half at night; maintenance dosage (on basis of prothrombin determinations daily for first three days), 50 to 100 mg. daily, divided as above.

Available on prescription through all pharmacies, in original bottles of 100 and 1000 50-mg. scored tablets.

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Natural bile acids *help restore* natural biliary function

- 'Bilron' contains natural conjugated bile acids combined with iron.
- 'Bilron'—a potent, true choleretic—produces bile of natural composition and consistency.
- 'Bilron' is chemically enteric. It is soluble in the alkalinity of the intestine, where bile is normally released.

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'Bilron' is indicated in gall-bladder-type indigestion, constipation, biliary dyskinesia, and following cholecystectomy.

PULVULES

'Bilron'

(IRON BILE SALTS, LILLY)

The American Journal of Medicine

Vol. XIV JUNE, 1953 No. 6

Editorial

Anticoagulant Therapy in Acute Myocardial Infarction

Following the report of the Committee of the American Heart Association which recommended the use of anticoagulant drugs in the treatment of coronary thrombosis[1] many investigators have confirmed the value of heparin and dicumarol® in reducing the incidence of thromboembolic complications in this disease and the mortality resulting therefrom. There is little doubt that in *severely ill patients* the anticoagulants have an important place in treatment; it is more difficult, however, to justify their routine use in *all* cases of coronary thrombosis.

Wright,[2] in supporting the Committee's contention that all patients should receive these drugs when no contraindications exist, claimed that experience is "replete" with examples of disabling or fatal thromboembolism occurring unexpectedly in the course of relatively mild attacks of acute myocardial infarction. This view is indeed in accord with statements found in most textbooks of cardiology which depict the outcome from acute coronary thrombosis as "unpredictable because of the constant threat of sudden unexpected death, even for persons convalescing favorably."

Some authors,[3–10] however, have criticized this grim characterization of the prognosis for milder cases and have challenged the value of anticoagulants in their management. In recent studies[3,4] 1,047 cases treated conservatively were separated into "good risk" and "poor risk" groups on the basis of information available on the day of admission to hospital. The signs considered to indicate a serious prognosis were a history of previous infarction, intractable pain, severe or persistent shock, cardiac enlargement, gallop rhythm, heart failure, arrhythmias and other states predisposing to thrombosis. In 489 patients in whom none of these factors were present the mortality during the period of hospitalization was only 3.1 per cent, compared with 60 per cent in the group showing one or more of these unfavorable signs. Analysis of the causes of death among the "good risk" patients indicated, moreover, that no more than one fatality in every hundred patients could have been prevented by dicumarol if the latter were capable of averting all thromboembolic complications. Of further significance was the finding that among "good risk" patients surviving

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forty-eight hours from the time of admission to the hospital, the subsequent death rate from all cardiovascular complications was only 1.2 per cent while the incidence of clinical thromboembolism was less than 1 per cent. Obviously these observations do not reflect the formidable risk of sudden death claimed to exist even with milder attacks nor do they confirm the view that thromboembolism is a significant cause of disability and death in such cases.

It has been maintained that old age provides a special indication for the use of anticoagulant drugs in cases of acute myocardial infarction. The patient over the age of sixty is commonly regarded as more vulnerable than the younger patient who has sustained an attack of similar severity. Recent studies indicate that no justification exists for this concept. Although statistically there is a relatively higher incidence of serious attacks among older patients, the prognosis for a severe attack or a mild one appears to be unaltered by age.[11] The initial clinical appearance of the patient would therefore seem to constitute the best index to his future course and the deciding factor regarding the need for anticoagulant therapy.

It has been suggested that anticoagulants may have additional life-saving actions beside that of preventing thromboembolism. Some have contended that these agents ward off congestive failure, ventricular fibrillation and asystole by preventing further clotting in the coronary lumen. Gilbert and Nalefski[12] have attributed the favorable results observed from the use of anticoagulant drugs in cases of acute myocardial infarction and angina pectoris primarily to an increase in coronary blood flow. Graham and associates,[13] on the other hand, in reporting marked relief of anginal symptoms in patients receiving periodic injections of heparin, ascribe the beneficial response to the profound effect of the drug on lipoprotein metabolism. Other studies with heparin, however, have failed to demonstrate either subjective improvement in anginal symptoms or favorable influence on the electrocardiographic response to standard exercise.[14] The recent report of Gilchrist[15] offers a possible explanation for the unexpectedly large benefits reported from the use of anticoagulant drugs. This author observed that the early and efficient use of heparin and dicumarol or tromexan appears to influence favorably the outcome of the shock syndrome. Deaths from the severer grades of shock were reported to have been reduced from 15 to 4 per cent as the result of therapy. Gilchrist suggests that the early employment of heparin in addition to the more slowly acting anticoagulants may limit the spread of multiple thrombotic extensions in and through the zone of demarcation separating the necrotic from the adjoining healthy muscle. Control of the thrombotic tendency may thus prevent an advance in the vicious cycle of thrombosis, infarction and hypotension. If these findings are confirmed, the current practice of administering dicumarol or tromexan alone without the immediate use of heparin must be viewed as falling far short of achieving optimum benefits from anticoagulant therapy in many cases.

Inasmuch as dicumarol has since 1947 become one of the most common causes of death due to drugs,[16] its employment for mild attacks of coronary thrombosis in which the risk of thromboembolism is small does not appear warranted. Major hemorrhage occurred in 1.9 per cent of 9,609 patients given dicumarol, according to a review of the literature,[17] and in 2 per cent of 15,500 patients treated with dicumarol and heparin by 136 physicians responding to a questionnaire.[18] In a recent survey[19] 228 cardiologists and internists reported a total of 122 deaths caused by hemorrhage from heparin or dicumarol in the treatment of myocardial infarction.

The wide employment of anticoagulant drugs

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in acute coronary thrombosis has been associated with another risk, commonly overlooked. In order to institute treatment without delay many patients are rushed to the hospital shortly after the onset of their clinical attack despite the fact that the highest death rate in this disease prevails during the first forty-eight hours. Since these early deaths are the result of ventricular fibrillation, cardiac asystole, shock or congestive heart failure, and are unrelated to thromboembolism, they almost certainly cannot be prevented by anticoagulant drugs. The desire to save the small proportion who may die from thromboembolism after the first week may therefore jeopardize the chances for survival of the much larger segment of coronary cases known to die from other causes during the first two days. For many patients, being jostled in an ambulance or admitting office, then subjected to the psychic trauma of a hospital room and bed, and of being placed in an oxygen tent, often when oxygen is entirely unnecessary, and being repeatedly punctured for prothrombin and coagulation times hardly constitutes optimum management during this early critical period. In most instances any form of treatment deemed necessary can be initiated in the patient's home and removal to a hospital can be accomplished, if indicated, when this critical period has passed.

Many physicians feel obliged to use an anticoagulant drug in every patient who sustains an attack of acute myocardial infarction. In some instances this attitude is based upon a firm personal conviction regarding the value of this form of treatment. In others it takes origin from the pronouncement of the American Heart Association's Committee that all cases should be treated in this manner. Many physicians who remain unconvinced or uncertain regarding the benefits to be derived from anticoagulant drugs continue their routine use chiefly because of fear of criticism by colleagues or of reproach by patients or their relatives who have learned of this form of therapy. Some physicians have candidly expressed real apprehension at the thought of possible litigation for malpractice if death or complications were to develop in their patients not receiving these drugs. From the evidence, however, anticoagulants like any other drug are indicated only under certain well defined circumstances. In acute myocardial infarction perhaps some 40 per cent of all cases may not require this form of treatment.

The days of "masterly inactivity" in the management of coronary thrombosis are being gradually replaced by a positive therapeutic program but it is well to remember that there is no disease in which overtreatment or disregard of physiologic concepts can prove more disastrous.

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Clinical Studies

Effect of Weight Reduction and Caloric Balance on Serum Lipoprotein and Cholesterol Levels*

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DETERMINATION of the role of weight reduction as a preventive and therapeutic measure in the control of atherosclerotic vascular disease is of considerable practical importance. Many physicians, health agencies and life insurance companies have sponsored programs designed to prevent and treat obesity. These programs advocate, in part, the achievement of desirable weight for the prevention of atherosclerosis. The validity of this belief that obesity is associated with and is presumably responsible for an increased prevalence of atherosclerosis has not been unequivocally demonstrated. While various actuarial experiences indicate that obesity is associated with health impairments,[1] this evidence has not adequately answered the question concerning the importance of weight reduction in the management of atherosclerosis. A recent study by Dublin and Marks[2] of a large group of overweight people who reduced their weight seems to support the contention that such a procedure is beneficial.

Lipid metabolism has been implicated to some degree in the development of atherosclerosis in experimental animals and in man.[3] There is widespread although not unanimous opinion that the serum levels of cholesterol and of certain lipoproteins are associated with and perhaps even causally related to the genesis of atherosclerosis.[4] The measurement of these serum lipids as a diagnostic method is, however, the source of much confusion because of the uncertainty of the relationship of the lipids to atherosclerosis.

There are at least two approaches to this complex problem. One is an extensive comparison of the levels of serum cholesterol and the implicated lipoproteins in obese and nonobese individuals. Data are available suggesting a positive relation between these lipids and obesity. One study has been reported by Gofman and Jones[5] who examined 241 normal American males aged forty-one to fifty years. Of these 199 were above desirable weight and 42 below. (Oddly, none were at their desirable weight.) It was concluded that the serum level of the S_f35–100 class of lipoproteins was significantly associated with weight, as was the level of the S_f12–20 class although to a lesser extent, whereas the serum cholesterol measurement had no significant relationship. In a study of 1,000 individuals thirty to sixty years of age, cited by Walker,[6] the relation of the S_f12–20 fraction to body weight revealed a progressive increase of this class of lipoproteins with increasing overweight. Furthermore, the increment of lipoprotein with increasing overweight was greater in males than in females. These data suggest that overweight may be associated with atherosclerosis. They cannot, however, establish a causal relationship until the true nature of the relation of the lipids to the disease is known, nor do the data prove the value of weight reduction in the mangement of atherosclerosis.

The second approach to this problem is

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through study of the effect of treating obesity, or more generally, the influence of loss of weight upon the implicated serum lipid constituents. This question has been considered by several workers[7,8] but for the most part weight reduction *per se* has not been the primary variable studied. The influence of low cholesterol, low fat diets upon the serum lipids has been repeatedly discussed[9,10] but weight reduction has generally been an additional variable not well segregated and studied.

The suggestive but inadequately documented impression that primitive and struggling societies in which obesity is rare are not prone to atherosclerosis,[11–13] and the indirect evidence supplied by an apparent decrease of mortality attributable to atherosclerosis during war-time restriction of food and thus of overweight[14–16] have tended to support the belief that the treatment of obesity would reduce the toll of atherosclerosis. There is, further, the evidence of Wilens[17] purporting to show that patients dying of a chronic body-wasting disease have less than the expected amount of atherosclerosis, thus implying that this vascular disease is reversible and that a period of caloric deficiency will effect this reversal.

We have investigated the influence of weight loss upon the serum cholesterol and certain classes of lipoproteins in a group of thirty-nine human subjects.

PROCEDURES

The subjects were selected primarily according to their willingness to lose weight and return for repeated observations. Twenty-nine of these subjects had cardiovascular disease which served to motivate their cooperation. The remaining ten were well except for obesity. The subjects' initial weights varied from "desirable," according to Metropolitan Life Insurance Tables,[18,19] to 50 per cent above desirable weight.

Twenty-eight of the subjects were male, eleven female. The ages ranged from twenty-nine to sixty-eight years. Ten were under forty years. No subject with edema was included and none was receiving medications other than phenobarbital and nitrites. No subject received heparin either during or immediately before the study. The subjects were all ambulatory outpatients. All the subjects were believed to have followed the regimen proposed and were able to lose 5 per cent or more of their respective weights during the course of the study.

Subjects were generally selected for the study without respect to their serum lipid levels. About one-fourth of the group, however, was selected in part because of elevated levels of serum lipoprotein in order that we might have a satisfactory range of initial values for evaluation. (Table I.)

TABLE I
DISTRIBUTION OF THIRTY-NINE SUBJECTS ACCORDING TO INITIAL SERUM LIPID LEVELS

Cholesterol, mg. %	<250	250–299	≥300
No. of subjects	14	11	14
S_f12–20, mg. %	0–49	50–79	≥80
No. of subjects	14	14	11
S_f35–100, mg. %	0–49	50–100	>100
No. of subjects	10	14	15

Diet. Twenty-nine of these subjects were known to have cardiovascular disease, and several reported some degree of cholesterol and fat restriction in their usual diets. In the beginning all subjects were asked to continue the diets to which they were accustomed while taking care to maintain their body weights. Control measurements were made during this regimen.

After this initial period, caloric restriction was begun on a diet containing approximately 1,000 calories with 100 gm. of protein, 50 gm. of fat and 100 gm. of carbohydrate. The daily ingestion of two eggs was required to insure a minimum daily intake of 600 mg. of cholesterol. By this device a relatively constant cholesterol intake was achieved throughout. The aim was to have the subjects lose at least 2 pounds per week. In four subjects amphetamine was given for brief periods in an effort to facilitate weight loss. The weight losing period was considered ended when a subject failed to lose more than ⅓ pound per week.

During the weight maintenance period the caloric intake was liberalized individually by additions to the carbohydrate and protein components of the diet. Fat and cholesterol intakes were continued unchanged. However, during this period seventeen subjects were instructed to cease the daily consumption of the two eggs and to avoid all other cholesterol-rich foods. This regimen was then continued for two months during which serum lipids were measured in an effort to evaluate the contribution of the egg lipids.

Laboratory Procedures. The subjects were seen throughout the study at monthly intervals or

more frequently. Body weights were measured under standard conditions of dress and these measurements were the ultimate criteria of adherence to the regimen.

At each visit blood was drawn for the serum analysis of total cholesterol by the method of

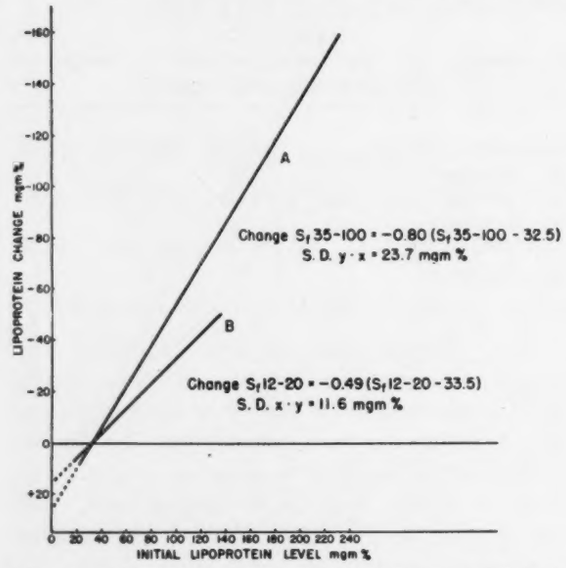
LIPOPROTEIN CHANGE mgm %
INITIAL LIPOPROTEIN LEVEL mgm %
A
Change Sf 35-100 = −0.80 (Sf 35-100 - 32.5)
S. D. y·x = 23.7 mgm %
B
Change Sf 12-20 = −0.49 (Sf 12-20 - 33.5)
S. D. x·y = 11.6 mgm %

FIG. 1. The relation of the change of $S_f12–20$ and $S_f35–100$ to the respective initial level of each quantity. The data of thirty-two subjects who completed the regimen are included. The interrupted portions of the lines are extrapolated.

Abell et al.[20] and lipoproteins of the $S_f12–20$, $S_f21–35$ and $S_f35–100$ classes by the method of Gofman et al.[21] Running duplicate analyses of either these or other human sera revealed the duplicate reproducibility shown in Table II.

TABLE II
REPRODUCIBILITY OF THE LABORATORY DETERMINATIONS EMPLOYED IN THIS STUDY

	Standard Error of Duplicates* (mg. %)
Total cholesterol	10.7
$S_f12–20$	4.9
$S_f21–35$	3.1
$S_f35–100$	7.7

* Standard error of duplicates $= \sqrt{\frac{\Sigma\Delta^2}{2K}}$ where K = number of pairs; Δ = difference between duplicate analyses

Blood samples were drawn in no constant relation to meals but were generally three or four hours post-prandial.

The control values obtained during the initial period consisted of two or more measurements in twenty-nine subjects and one measurement in each of the remaining ten subjects. During the weight-losing period serum was obtained at two- or three-week intervals and at one- to two-month intervals during the weight maintenance period.

The subjects have been followed for periods of two to sixteen months with an average of eight months, comprising in all 312 subject-months of observation.

RESULTS

It was not possible to induce each subject to reduce his weight to the desirable level. The group accomplished and maintained a weight loss varying from 7 to 40 pounds each with an average loss of 19 pounds. The relation of the thirty-two subjects who completed the regimen to their desirable weight at the start and finish of the regimen is shown in Table III.

TABLE III
DISTRIBUTION OF THIRTY-TWO SUBJECTS ACCORDING TO THE RELATION OF THEIR BODY WEIGHT TO DESIRABLE WEIGHT

Relative Weight*	No. of Subjects	
	Start	Finish
0.91–1.00	0	15
1.01–1.10	13	9
1.11–1.20	8	6
1.21–1.30	6	0
1.31–1.40	3	2
1.41–1.50	2	0

* Relative weight is expressed as the ratio of the observed weight to the desirable weight.

The rate of weight loss among the thirty-nine subjects varied considerably. In all, the duration of the weight-losing period varied from 15 to 277 days with a mean of 106 days. The average time required by the thirty-two subjects who completed the three phases of the study to lose half the total weight loss achieved was 40.5 days. The mean loss per day was 0.235 pounds (1.6 pounds/week).

Weight loss was in most although not all subjects associated with a reduction of all three categories of serum lipoproteins. This reduction of lipoproteins was most marked for the $S_f35–100$ categories but was significant for the $S_f12–20$ and 21–35 as well. The lipoprotein changes were, however, subject to marked individual variation. Table IV indicates the distribution of

responses among the thirty-nine subjects studied. There was no relation between the amount of weight loss and the changes of serum lipids.

Thirty-two subjects accomplished all three phases of the study, i.e., control, losing and maintenance. Data for each period in Table v represent the averages of all measurements made during the respective period. These subjects, who lost on the average 12 per cent of their desirable weight, significantly reduced their $S_f12–20$, 21–35 and 35–100 classes of lipoproteins. The cholesterol reduction was not statistically significant at the 5 per cent level.

impression the regression lines relating the net lipoprotein changes from the control phase to the weight maintenance phase with the initial levels were computed. A significant relationship was found. (Fig. 1.) The regression equation for the $S_f12–20$ class indicates that only those subjects with initial $S_f12–20$ levels greater than approximately 50 mg. per cent (i.e., 33.5 + 11.6) can be expected to reduce their levels by weight reduction. Similarly, only those subjects with initial $S_f35–100$ levels greater than 60 mg. per cent (32.5 + 23.7) can be expected to lower their $S_f35–100$ levels with weight reduction.

TABLE IV

RESPONSE OF THE SERUM LIPIDS OF THIRTY-NINE SUBJECTS WHO LOST 5 PER CENT OR MORE OF THEIR DESIRABLE WEIGHTS*

Weight Loss (lb.)	No. of Subjects	$S_f12–20$ (mg. %)		$S_f21–35$ (mg. %)		$S_f35–100$ (mg. %)		Total Cholesterol (mg. %)	
		Start	Finish	Start	Finish	Start	Finish	Start	Finish
6–10	6	51	33	28	20	66	32	271	232
11–15	13	54	50	29	23	73	39	284	262
16–20	9	82	53	49	18	93	18	255	251
21–30	8	59	49	32	26	119	52	317	297
31–40	3	60	54	31	19	85	28	299	311
	39	Means 61.5	48.2	34.4	22.0	86.8	34.8	283	266

* Data represent the lipid changes occurring between the control and the end of the weight-losing phase of the regimen.

TABLE V

PERFORMANCE OF THIRTY-TWO SUBJECTS WHO COMPLETED THE WEIGHT-LOSING REGIMEN

	No.	Relative Weight	$S_f12–20$ (mg. %)	$S_f21–35$ (mg. %)	$S_f35–100$ (mg. %)	Cholesterol (mg. %)
Control	32	1.16	64.2	37.1	93.0	278
Losing	32		49.9	22.3	36.6	264
			$p < 0.05$*	$p < 0.01$	$p < 0.01$	$p > 0.05$
Maintenance	32	1.04	49.1	23.2	44.5	261

* The symbol "p" indicates the probability that this observed difference is a chance occurrence. Throughout this discussion differences with a chance probability of 0.05 or less are taken to be significant. Values of "p" were obtained by the application of a standard "t" test.

It was also apparent that the serum lipid reductions were already maximal at the end of the losing phase of the study.

It appeared that subjects with initially elevated lipid levels experienced greater reduction of these levels with weight loss. To confirm this

The regression lines also show that the influence of weight loss in lowering these lipid components is such that individuals maintain their position in a rank made according to initial levels; i.e., a person with an initial $S_f12–20$ level of 100 mg. per cent can expect to reach

70 mg. per cent whereas one with an initial level of 80 mg. per cent can expect to reach 60 mg. per cent. In order to take this into account it was convenient to divide the thirty-two subjects into three groups according to initial $S_f12–20$ levels. Such a procedure does not rank subjects perfectly in respect to the other lipid components but, in general, persons with high $S_f12–20$ levels also have high $S_f20–100$ and high cholesterol levels, as the data of Table VI indicate. When studied in this fashion the three groups were well matched in respect to number of subjects, rate of weight loss and initial and final relative weights. The $S_f12–20$, 21–35 and 35–100 classes of lipoproteins were significantly reduced during the weight-losing period in Groups I and II with initial $S_f12–20$ levels of 50 mg. per cent or higher. However, these lipoprotein classes were not reduced in Group III with initial $S_f12–20$ levels below 50 mg. per cent nor were the serum cholesterol levels significantly reduced at the 5 per cent level of probability in any of the three groups. Furthermore, the degree of reduction of each

TABLE VI

RESPONSE OF SERUM LIPOPROTEIN AND CHOLESTEROL LEVELS IN THIRTY-TWO INDIVIDUALS LOSING WEIGHT, WHEN GROUPED ACCORDING TO INITIAL $S_f12–20$ LEVELS

Period	Relative Weight	Rate of Weight Loss Av. Days Losing	$S_f12–20$ (mg. %)	$S_f21–35$ (mg. %)	$S_f35–100$ (mg. %)	Cholesterol (mg. %)
Group I $S_f12–20 \geq 80$ mg. % No. = 10						
Control	1.16	103.7	99.0	56.2	120.5	319
Losing	....	.....	69.6 $p < 0.01$	26.0 $p < 0.01$	28.7 $p < 0.01$	291 $p > 0.2$
Maintenance	1.03	.....	65.9	25.8	37.0	279
Group II $S_f12–20$ 50–79 mg. % No. = 12						
Control	1.16	112.9	63.9	34.3	90.2	269
Losing	....	.....	51.5 $p < 0.02$	23.8 $p < 0.05$	46.5 $p < 0.05$	262
Maintenance	1.03	.....	53.0	25.8	57.3	270
Group III $S_f12–20 < 50$ mg. % No. = 10						
Control	1.17	99.7	29.6	21.4	68.8	247
Losing	....	.....	28.3 $0.2 < p < 0.3$	16.9 $0.2 < p < 0.3$	32.7 $0.1 < p < 0.2$	239 $0.05 < p < 0.1$
Maintenance	1.05	.....	27.8	17.5	36.7	231

TABLE VII

CHANGE OF SERUM LIPID LEVELS OCCURRING WITH WEIGHT REDUCTION CONSIDERED ACCORDING TO THE INITIAL LEVEL OF $S_f12–20$

Group	Initial $S_f12–20$ (mg. %)	No.	Change $S_f12–20$ (mg. %)	Change $S_f35–100$ (mg. %)	Change Cholesterol (mg. %)
I	≥80	10	−33.1 $p < 0.01$	−83.5 $p < 0.05$	−39.9
II	50–79	12	−11.0 $p < 0.01$	−32.19 $p < 0.05$	+ 1.4
III	<50	10	− 1.8 $p < 0.05$	−32.1	−16.9

class of lipoprotein was significantly greater in Group I with initial $S_f12–20$ levels of 80 mg. per cent or more than in Group II with lower levels. (Table VII.) It was apparent that further evaluation of the data must consider that individuals respond according to their initial loss was thus greater in individuals with high initial levels of either serum cholesterol or the $S_f12–20$ class of lipoprotein.

That the lowering of the various lipid components was accomplished early in the weight-losing phase and reached minimal values at this

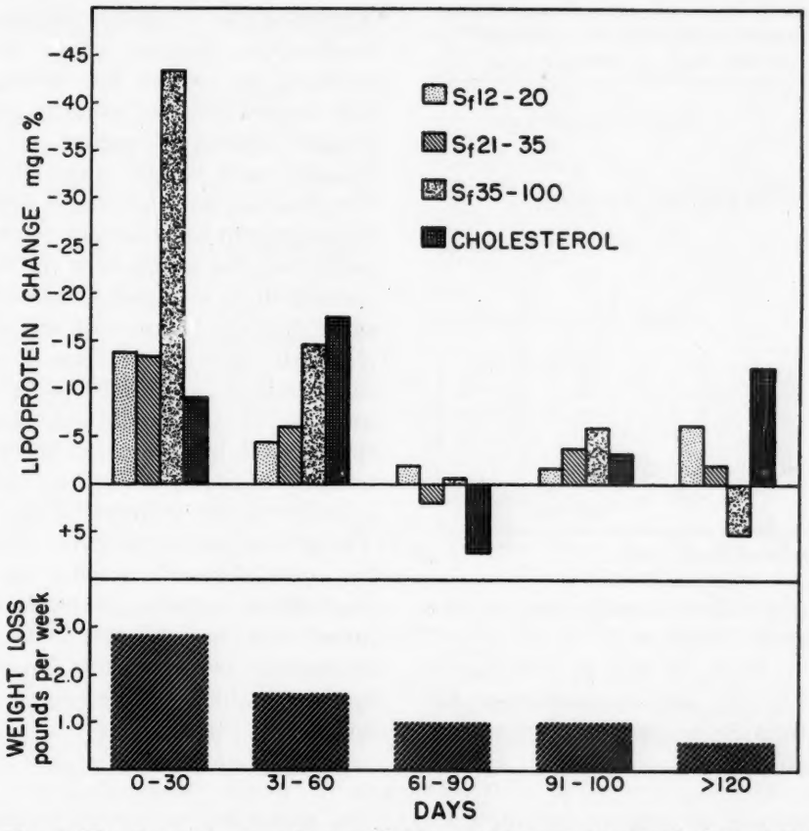

FIG. 2. The change in several serum lipid quantities associated with the weight reduction and the rate of weight loss. The data are mean values for twenty-five subjects with initial $S_f12–20 \geq 50$ mg. per cent.

$S_f12–20$ level and should be segregated according to this characteristic.

A similar analysis of the thirty-two subjects who completed the study, grouped according to their initial serum cholesterol values, has been made. A group of eleven subjects with initial serum cholesterol values ≥ 300 mg. per cent showed a significant drop of serum cholesterol, $S_f12–20$ and $S_f35–100$ during the losing phase. There was a significant reduction of the $S_f12–20$ for the group with initial cholesterol levels of 250–299 mg. per cent, but no real reduction of the cholesterol or $S_f35–100$. There was no reduction in any of the three lipoprotein classes in the group with initial cholesterol values under 250 mg. per cent.

The sensitivity of the serum lipids to weight time is indicated in Figure 2. The minimum values reached were in the range of values expected for normal subjects of similar age and sex.

These observations prompted an assessment of the relation of the rate of weight loss to the behavior of lipid levels. The analysis is shown in Table VIII. When all thirty-nine subjects were classified according to the rate at which they had lost weight between the last control observation and the first observation during the reducing period, there were twenty-three who had lost at a rate of more than 2 pounds/week and sixteen at a rate of less than 2 pounds/week. Comparison of the lipoprotein and cholesterol level changes accomplished during these losing periods revealed no significant differences at the

5 per cent level of probability. Since it has been established that subjects with low initial levels of $S_f12–20$ do not lower their lipid levels with weight loss, the same comparison of degree of lipid change with rate of weight loss was made according to our previous classification by the initial $S_f12–20$ level. (Table IX.)

TABLE VIII
DEGREE OF CHANGE OF SERUM LIPID COMPONENTS OBSERVED IN THIRTY-NINE SUBJECTS COMPARED ACCORDING TO THE RATE OF WEIGHT LOSS

	Rate of Weight Loss		
	>2 lb./wk.	<2 lb./wk.	Sig. p
No. of Subjects	23	16	
Δ* $S_f12–20$	−13.1	− 9.2	n.s.
Δ $S_f35–100$	−59.0	−29.5	$p \sim 0.1$
Δ Cholesterol	+ 3.6	−26.3	$p > 0.05 < 0.10$
Mean weight loss (lb./wk.)	3.8	1.2	

* Δ indicates change of level in mg. %.

The subjects in Group I and II with initial $S_f12–20$ levels of 50 mg. per cent and above did not alter their $S_f12–20$ levels differently when compared according to their rate of weight loss. Those losing at a rate of greater than 2 pounds per week did lower their $S_f35–100$ class of lipoproteins more than did those losing at a rate of less than 2 pounds per week. The rapid losers, paradoxically, showed less change of the serum cholesterol than did the slow losers.

This demonstration of an influence of rapid weight loss suggested that the serum lipids might bear some relation to caloric balance. Such an effect has been demonstrated for the serum cholesterol in short term experiments.[22] If such a relationship of caloric balance to serum lipid levels exists, positive caloric balance would be expected to elevate the serum lipids. To test this hypothesis two normal adult males were studied during a period of positive caloric balance with weight gain while consuming a very low fat, low cholesterol diet. (Fig. 3.) After measurement on a weight maintenance control period of two weeks with the low fat, low cholesterol diet, a period of forced feeding of the same diet was begun with the aim of producing a weight gain of at least 1 pound per day. Subject D. L. gained 10 pounds in eleven days and W. W. 11 pounds in nine days. During this period both showed a two- to threefold increase of the $S_f12–20$ class of lipoproteins and a much larger increase of the $S_f35–100$ class. The serum cholesterol levels showed a significant but more delayed rise with the period of positive caloric balance. Since the diets used contained less than 15 gm. of fat and 50 mg. of cholesterol per day, this increment of serum lipids must be attributed to an increase of non-fat calories.

TABLE IX
INFLUENCE OF RATE OF WEIGHT LOSS ON SERUM LIPIDS, ACCORDING TO INITIAL LEVEL OF $S_f12–20$

	Groups I and II (Initial $S_f12–20 \geq 50$ mg. %)			Group III (Initial $S_f12–20 < 50$ mg. %)		
Rate of loss	>2 lb./wk.	<2 lb./wk.		>2 lb./wk.	<2 lb./wk.	
No. of subjects	13	12	p	10	4	p
Days losing	15	41		16	45	
Δ* $S_f12–20$	−25.1	−11.4	>0.1	+ 2.4	− 2.5	n.s.
Δ $S_f35–100$	−84.4	−37.5	<0.05	−26.0	− 5.5	n.s.
Δ Cholesterol	+ 3.3	−40.1	<0.05	+ 3.6	−36.5	>0.1
Mean weight loss (lb./wk.)	3.6	1.2		4.1	1.2	

* Δ indicates change of level in mg. %.

A further assessment of the role of dietary cholesterol in the control of serum lipid levels was made in twenty of the subjects who had reached and stabilized in the third, or weight maintenance, phase of this study. These subjects

who had previously consumed two eggs per day were asked to avoid all eggs and cholesterol-containing foods for two months. Serum obtained for measurement at the end of the first and second months of this period of restricted cholesterol intake gave the results shown in Table x. None of these differences are significant at the 5 per cent level of probability which indicates that under these conditions the cholesterol intake was not a determining factor in the serum lipids measured.

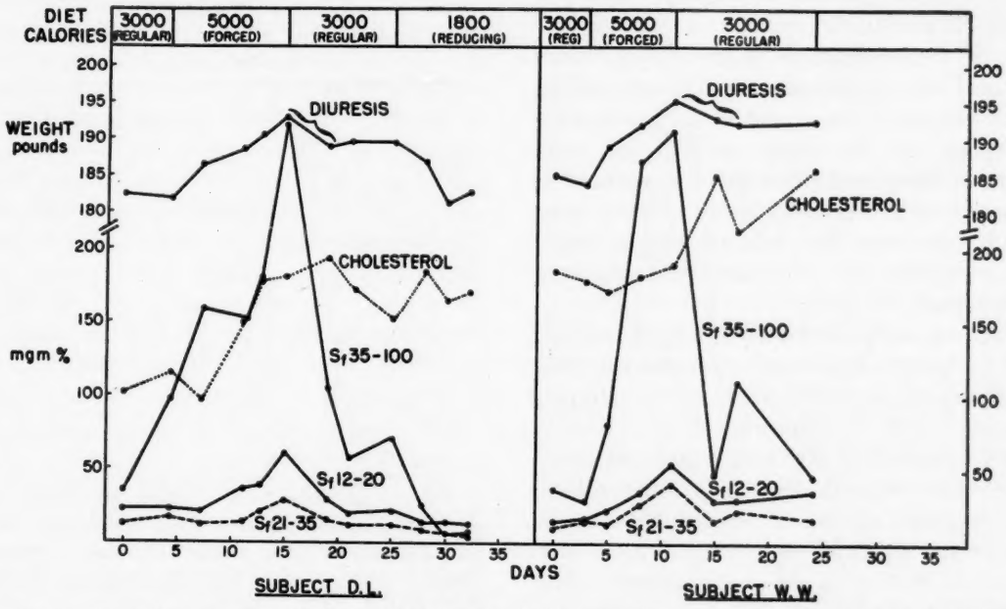

FIG. 3. The effects of a period of forced feeding of calories upon the serum lipids of two normal adults. The diet throughout was very low in fat and cholesterol. The serum measurements are means of duplicates.

Two of the subjects died during the course of the study. Each of these was among the twenty-nine subjects known to have cardiovascular disease at the start of the study.

TABLE X
EFFECT OF RESTRICTING CHOLESTEROL INTAKE ON THE SERUM LIPIDS OF TWENTY SUBJECTS ON A LOW FAT, LOW CHOLESTEROL DIET

Cholesterol	Duration (days)	S_f12–20 (mg. %)	S_f35–100 (mg. %)	Cholesterol (mg. %)
Liberal intake 600 mg./day.....	57 Range (26–119)	55.3	48.4	279
Low intake 100 mg./day.....	53 Range (20–120)	52.4	47.0	259

Subject A. D., a fifty year old white male, had well established angina pectoris of six years' duration. The angina forced moderate restriction of activity. The ballistocardiograph was abnormal, the electrocardiograph normal. This man's relative weight was 1.36 at the start of the study, his serum cholesterol was 323 mg. per cent and serum lipoproteins were S_f12–20, 60 mg. per cent, S_f21–35, 33 mg. per cent and S_f35–100, 97 mg. per cent. On the weight losing regimen a steady weight loss of approximately 2 pounds per week was maintained for twelve weeks. Four successive measurements of serum lipids revealed a downward trend in all these quantities, the final values two weeks before death being cholesterol 286 mg. per cent, S_f12–20, 48 mg. per cent, S_f21–35, 29 mg. per cent and S_f35–100, 42 mg. per cent. Although an autopsy was not obtained, the clinical events indicated that the sudden death was caused by a myocardial infarction.

Subject H. E. was a sixty-three year old white male who was known to have had a moderate degree of hypertension for six years. Four years prior to the present study the subject had a well documented myocardial infarction. Two years previously he had shown evidences of a minor cerebrovascular accident. This man's relative weight was 1.05 at the start of the present study; his serum cholesterol was 296 mg. per cent and the serum lipoproteins S_f12–20, 61 mg. per cent, S_f21–35, 43 mg. per cent and S_f35–100, 87 mg. per cent. On the weight-losing regimen this man's weight loss was only 11 pounds in 150 days. Five successive lipid measurements during

this weight losing revealed a decrease for the first eighty-five days to minimal values, followed by a steady increase thereafter which continued into the weight maintenance period and reached maximal values ten days before death when they were: cholesterol 265 mg. per cent, $S_f12–20$, 70 mg. per cent, $S_f21–35$, 43 mg. per cent and $S_f35–100$, 89 mg. per cent.

Each of these subjects with known heart disease had accomplished a significant weight reduction. In one subject the serum lipids were also reduced; in the other subject an early reduction of lipids was followed by a rebound to levels equal to the control levels. There is no means of assessing the relationship of these clinical events to the procedure or laboratory measurements.

The permanency of the serum lipid changes induced by weight loss is an important criterion of the effectiveness of this treatment in altering the serum lipids. Evaluation of this feature requires evaluation of the individual responses, since the mean response of a group of individuals may be typical of none. Assessment of the changes in the lipid levels of any individual is complicated by the day-to-day biologic variability of that individual as well as by the technical error of measurement.

Since the uncertainty of measurement caused by technical error has been measured, this information can be used to estimate a minimal change of lipid level that is not likely to be due to chance. With a standard error of measurement of the $S_f12–20$ class of 4.9 mg. per cent, two separate, single determinations on a given person may be expected to differ by $\pm\sqrt{2} \times 4.9 = \pm 6.9$ mg. per cent because of technical error alone.[23] If, however, we have available not single determinations but the average of several, this error will be reduced. A study of the extent of biologic variability currently underway in this laboratory[24] suggests that it would be more reasonable to consider that a difference of less than $\pm$ 10 mg. per cent in the $S_f12–20$ levels is not real.

With this criterion for a real change, twenty-one of the thirty-two persons who completed the study had final $S_f12–20$ levels less than their initial levels, nine persons showed no change and two persons showed an increase. (Table XI.) The levels of all ten of the persons in Group I (initial $S_f12–20 \geq 80$ mg. per cent) decreased, eight of those in Group II decreased and the other four showed no change. In Group III, three showed decreases, five no change and two increased. In seventeen of the twenty-one persons showing net decreases both the weight-losing and weight-maintenance levels were less (by ≥ 10 mg. per cent) than the control levels. However, three of the twenty-one, while showing a reduction of 10 mg. per cent or more during the losing phase, increased their levels by 10 mg. per cent or more when they stopped losing weight. This phenomenon of a decrease followed by an increase we have designated as a "rebound." One subject showed a weight-losing level higher than his control level. Of the nine showing no net change, two had weight-losing levels less than the controls but rebounded to the initial levels; the other seven showed no change throughout the whole study. The two who increased did so uniformly (within the 10 mg. per cent limits). The initial $S_f12–20$ levels of these were 20 and 23 mg. per cent.

TABLE XI
NET CHANGES* IN $S_f12–20$ OF THIRTY-TWO SUBJECTS COMPLETING WEIGHT LOSING

Group	Initial Levels (mg. %)	No. of Subjects		
		Decrease	No Change	Increase
I	80	10 (2R)†	0	0
II	50–79	8 (1R)	4 (2R)	0
III	50	3	5	2
	Totals	21	9	2

* A change of $\pm$10 mg. % or more between the control and maintenance phases was used in this evaluation.
† (R) indicates the number of subjects who after an initial lowering of their $S_f12–20$ level later increased this level 10 mg. % or more.

It is clear then that subjects with the highest initial lipoprotein levels obtain the largest decrease of their levels with weight loss and further that the permanency of this change is in proportion to the initial level. No other clue has been found which will aid in predicting the direction, the magnitude or the permanency of the serum lipid change with weight loss.

COMMENTS

This study has demonstrated that in many individuals serum lipoprotein levels are sensitive to the status of caloric balance. The serum lipids

tended to fall during negative caloric balance and to rise when this was positive. These observations, taken in conjunction with earlier studies indicating a positive correlation between body weight and lipoprotein levels, support the several contentions relating nutritional status to atherosclerosis. Thus the supposed rarity of atherosclerosis in lean and hungry societies, the diminution of atherosclerosis in cachexia, the improved health performance of people who lose weight and possibly the low lipoprotein levels seen during the acute phase of a myocardial infarction may all be related to this phenomenon.

This study does not exclude the dietary lipids as influential in the control of the serum lipids, for the weight-losing phase was coincidental with a drastic restriction of dietary lipids other than cholesterol. A study accomplishing weight reduction on a high dietary lipid intake is necessary. This study reveals no evidence that the cholesterol content of the dietary lipids limits or even influences the alteration of serum lipids accomplished by weight reduction.

Several interesting implications are posed by these data. When the data were grouped and studied according to the initial degree of obesity as expressed by the relative weight, there was no correlation of this measure with the response of the lipids to weight loss. Thus the influence of weight loss upon the serum lipids was not determined by the degree of initial obesity.

Both the rate of weight loss and rate of lipid reduction were maximal in the early part of the weight-losing period. A moderate but statistically significant correlation between rate of weight loss and degree of lipid reduction could be shown in the entire group. As suggested in the regression lines, while those subjects with high initial levels of $S_f12–20$ did show the largest reductions with weight loss, the subjects did not reach a common level. After the reduction of weight and serum lipids the subjects largely maintain their original ranking according to $S_f12–20$ level. These data suggest that caloric insufficiency or weight loss represents only one component of the total regulation of serum lipoprotein and cholesterol levels.

The performance of these subjects indicated that starting with an unselected group with known initial levels of $S_f12–20$ several responses are possible. The best predictive evidence is the initial $S_f12–20$ level and not the degree of obesity nor even the rate or degree of weight loss accomplished. Even among subjects with initial $S_f12–20$ levels of ≥ 50 mg. per cent a significant number will be found who will either not change their lipoprotein levels with weight loss, or will after a change show a rebound of levels either partially or completely cancelling the initial reduction. Among subjects with initial levels of <50 mg. per cent the response is more heterogeneous and includes a few who show an actual increase.

The correlation between obesity and serum lipoprotein levels coupled with this demonstration that weight reduction will often lower these serum lipoproteins suggests that in our present state of knowledge the prevention and correction of obesity is the most plausible treatment of atherosclerosis. This approach would be strengthened if a positive correlation between the serum lipids and the causation of atherosclerosis were established.

CONCLUSIONS

1. An average weight loss of 19 pounds in thirty-nine subjects led to a significant reduction of the serum $S_f12–20$, $S_f21–35$, $S_f35–100$ and total cholesterol in the majority of instances.

2. The degree and permanency of this serum lipid reduction can be related to the initial level of $S_f12–20$. The influence of weight loss in reducing serum lipids is greater and more consistent in subjects with initial lipoprotein levels of 50 mg. per cent or more. In subjects with lower levels no reduction, a reduction followed by a rebound, or even increases of serum lipids are observed with weight loss.

3. The degree of initial obesity is not a determining factor in the serum lipid changes and the rate of weight loss seems only slightly concerned.

4. Strong positive caloric balance in two subjects on a very low lipid intake was associated with significant increases of the serum cholesterol and lipoproteins. Thus caloric balance appears to play a major role in controlling these serum lipid levels.

5. On a low fat diet the cholesterol intake had no demonstrable influence upon the serum lipids.

6. If elevated serum lipid levels contribute to the causation of atherosclerosis, weight reduction is a proper treatment for this disease.

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Hypercholesterolemia, Myxedema and Atherosclerosis*

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In the extensive literature on the relation between atherosclerosis and lipid metabolism the statement is repeatedly made that myxedema with its hypercholesterolemia induces atherosclerosis. The supporting evidence for this assertion is incomplete and inconclusive.[1]

Our studies of the therapeutic effect of hypothyroidism induced to alleviate intractable angina pectoris and congestive failure provide a unique opportunity to examine this question.[2–4] The purpose of the present communication is to report the clinical findings and postmortem observations in a group of patients who survived one to thirteen years following surgical total thyroidectomy and in whom hypometabolism or myxedema with increased cholesterol values was present. The results demonstrate that progressive atherosclerosis of the coronary arteries is not a necessary concomitant of increased blood cholesterol levels in hypothyroidism or of the hypothyroid state.

Our observations have been made in patients with rheumatic heart disease and cor pulmonale and thus afford particularly important evidence.[5] In them, particularly in the younger age group, only slight or minimal coronary arteriosclerosis would ordinarily be anticipated at death. If prominent atherosclerotic lesions were observed post mortem, they might well be attributable to the myxedematous state. Conversely, the absence of abnormal atheromatosis after prolonged hypometabolism indicates that hypercholesterolemia or hypothyroidism does not necessarily lead to atheromatosis over the period of years during which our patients survived. These same considerations do not apply to the majority of patients in whom total thyroidectomy was induced for the alleviation of angina pectoris due to coronary arteriosclerosis. In such patients extensive severe narrowings and occlusions of the coronary arteries are observed post mortem in the absence of hypothyroidism[5–7] and the possible effect of concomitant associated hypothyroidism cannot be evaluated.

METHODS

In the patients in the Beth Israel group, blood for cholesterol measurements was drawn from the antecubital vein, with minimal stasis, after a fast of fourteen hours or more. Measurements of serum cholesterol were made in duplicate by the method of Myers and Wardell,[9] using the apparatus for continuous extraction described by Ling.[10] The averages of the duplicate measurements, which checked within 5 per cent, have been reported. The high limit accepted for normal serum cholesterol values is generally about 230 mg. per 100 cc. by this method. In the patients studied at the Peter Bent Brigham Hospital the cholesterol measurements were determined in the routine clinical pathologic laboratories by the method of Bloor.[12]

When weakness of the legs, drowsiness, emotional irritability or puffiness of the face developed, thyroid substance was administered in appropriate amounts to alleviate these untoward symptoms of myxedema without raising the basal metabolic rate sufficiently to place an undue burden on the heart. The amounts of thyroid substance administered were so adjusted as to maintain the patient in a hypothyroid state, as evidenced by dry skin, increased sensitivity to cold and a low basal metabolic rate.

As the basal metabolic rate decreased in our patients, following total ablation of the thyroid, the serum cholesterol concentration increased.

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In each patient clear evidence of hypothyroidism was present, as shown by clinical symptoms and signs, basal metabolic rate and increased serum cholesterol values. In each patient the degree of hypothyroidism, as indicated by the clinical symptoms and signs and the basal metabolic rate, was related to the *increase* in serum cholesterol concentrations rather than to the absolute cholesterol value. Thus in some patients with marked hypothyroidism who showed an increase of 100 or more mg. per cent the values were not much higher than those obtained in other patients when they were euthyroid. The average increase of 125 mg. above the average pretreatment levels of 170 mg. corresponded to a metabolic rate of minus 28 per cent in the large group of patients studied by Gilligan, Volk, Davis and Blumgart.[11] In each of the Beth Israel Hospital cases the cholesterol levels were above the generally accepted upper limit of normal of 230 mg. by the method used at the Beth Israel Hospital. In three of the Beth Israel Hospital cases and in two at the Peter Bent Brigham Hospital the cholesterol levels were markedly elevated above 300 mg. per cent.

CASE REPORTS

CASE I.* F. C., was a male, forty-one years of age. Total thyroidectomy was performed in 1933 when the patient was thirty-one years of age. He had had bronchial asthma since infancy and cor pulmonale with chronic incapacitating right ventricular failure during the five years before treatment. Physical examination showed conspicuous cyanosis, dyspnea, evidences of advanced pulmonary emphysema, slight enlargement of the heart, regular rhythm and no murmurs. The blood pressure was 120/70. Following total thyroidectomy the patient showed marked improvement for one year followed by recurrent attacks of asthma and congestive failure during the ensuing ten years. There was no evidence of rheumatic, syphilitic or hypertensive cardiovascular disease. He showed clear clinical and laboratory evidences of myxedema throughout the ten years of his survival until death at the age of forty-one years. (Table I.) He had received small amounts of thyroid (6 to 15 mg. daily).

Postmortem examination disclosed a moderate number of atheromatous plaques in the intima of the pulmonary conus and aorta. None of the atheromas showed ulcerations. All of the heart valves were thin, translucent and intact. The coronary arteries were not palpable. The left descending coronary and the left circumflex coronary arteries were not narrowed and there was no evidence of atheromatous changes or of any narrowing in these coronary arteries or their branches. The right coronary artery showed a moderate degree of atheromatous change throughout the main branch and its smaller tributaries. One of the plaques measured 0.5 by 1.0 by 0.2 cm. However, it was elevated only 0.2 cm. None of the atheromatous areas showed ulceration. The myocardium throughout both ventricles showed no evidence of softening or fibrosis. Examination of the neck revealed a few minute remnants of thyroid tissue which showed follicles dilated and congested with colloid. The lining epithelium had become extremely flattened. No morphologic evidences of activity were seen.

CASE II.* B. Z. This female patient, age forty-nine, with rheumatic heart disease and severe congestive failure was operated on in 1933. Physical examination at that time showed cyanosis, venous congestion, greatly enlarged heart, the characteristic signs of mitral stenosis and insufficiency, auricular fibrillation, congestion of the lungs and liver, marked edema of the legs and back. Following operation this patient showed striking improvement for two years, following which she developed ascites requiring frequent abdominal paracenteses. A diagnosis of cardiac cirrhosis of the liver was made. During the seven years of life after total thyroidectomy there was undoubted clinical hypothyroidism with elevation of the serum cholesterol values. The two thyroid nodular remnants disclosed at postmortem examination were apparently not of functional importance.

At postmortem examination slight pituitary hyperplasia, as described by Altschule and Cooper[8] in myxedema, was observed. Examination of the heart showed mitral stenosis and insufficiency, aortic insufficiency, cardiac hypertrophy and dilatation. The coronary arteries did not appear unusually firm or tortuous. The main left anterior descending artery showed approximately six slightly raised atheromatous patches beneath the endothelium, none of which produced evident narrowing. One such plaque

* This case is described in greater detail elsewhere (Case 10).[3]

* This case is described in greater detail elsewhere (Case 6).[3]

TABLE I

CLINICAL AND PATHOLOGIC DATA IN PATIENTS AFTER TOTAL THYROIDECTOMY

Clinical Data								Pathology Data									
			Postoperative Data						Coronary Arteries								
						Clinical Myxedema			Occlusions		Narrowing						
Case, Age, Sex	Diagnosis	Date Operation, Preoperative B.M.R., Cholesterol	Mo.	B.M.R. (%)	Cholesterol (mg. %)	Duration (yr.)	Severity	Heart Weight (gm.)	Old	Fresh	Left	Right	Circ.	Atheroma	Aorta	Pulmonary Artery	Cerebral Artery
															Atherosclerosis		
*Beth Israel Hospital Cases**																	
I, F. C. 41, M	Bronchial asthma, cor pulmonale, congestive heart failure	4/18/33 −4% 154 mg. %	2 6 8 38 40–80 99	−32 −27 −37 −23 −20 to −30 −18	217 255 216	10	Moderate	640	0	0	0	+	0	Slight	Moderate	Moderate	
II, B. Z. 49, F	Rheumatic heart disease, mitral stenosis and insufficiency, congestive heart failure	4/8/33 −5% 167 mg. %	1 3 6 9 12 20 53	−20 −27 −20 −21 −16	214 250 408 448 397 320 310	7	Moderate	776	0	0	0†	+	0	Slight	Moderate	Severe	0
III, G. F. 63, M	Rheumatic heart disease, congestive heart failure	12/15/32 −2% 255 mg. %	1 3 6 12 24 88	−23 −26 −25 −26	328 286 303 421	11½	Severe	610	0	0	+	0	+	Slight	Severe	Severe	Slight
IV, F. Z. 22, M	Rheumatic heart disease, mitral stenosis and insufficiency, aortic insufficiency, congestive heart failure	9/14/33 +1% 138 mg. %	½ 4 6 12	− 8 −10 −18 −19	199 254 246 231	1	Moderate	900	0	0	0	0	0	None	Severe	None	None
V, H. G. 28, M	Rheumatic heart disease, mitral stenosis and insufficiency, congestive heart failure	8/26/33 +8% 138 mg. %	1 2 6 14 33 48 56 68	−21 −27 −38 −41 −31 −30 −31	204 251 236 297 272 454	6	Severe	825	0	0	0	0	0	Moderate	Moderate	Severe	
Peter Bent Brigham Hospital Cases‡																	
VI, P. R. 44, F	Rheumatic heart disease, mitral stenosis, congestive heart failure	1/27/34 +16% 273 mg. %	1 3 8 15 34 48	+ 1 −20 −23 −11 −23 −22	368 305 230	4	Moderate	480	0	0	0	0	0	None	Slight	None	None
VII, M. A. 46, F	Rheumatic heart disease, mitral stenosis and insufficiency, congestive heart failure	4/25/34 −4% 155 mg. %	1 13 20 38 48 68 90	−24 −30 −13 −25 −20 −26 − 5	183 422 193 218	7	Moderate	560	0	0	0	0	0	None	Thoracic slight; abdominal moderate	Slight	None
VIII, A. P. 58, M	Rheumatic heart disease, mitral stenosis and insufficiency, aortic stenosis and insufficiency, congestive heart failure	2/12/34 −5% 300 mg. %	1 2 13 23 43 51 67 93 158	−19 −21 −25 −34 −36 −25 −28 −30 + 1	524 280 375	13	Moderate Severe, PBI 0.4 gamma %	610	0	0	0	0	0	Slight	Moderate	Moderate	None

* The cholesterol measurements were made in duplicate by the method of Myers and Wardell[9] using the apparatus for continuous extraction described by Ling.[10] The averages of the duplicate measurements, which checked within 5 per cent, are used.[11] The upper limit of normal values observed in euthyroid persons was 230 mg. per 100 cc.

† Left descending artery: few small patches without narrowing. Right coronary artery: one plaque with slight narrowing.

‡ The cholesterol measurements were determined in the routine clinical pathologic laboratories of the Peter Bent Brigham Hospital in 1934–38 by the method of Bloor.[12]

slightly narrowed the right coronary artery to a diameter of approximately 3 mm. a short distance beyond the origin of the vessel. No subintimal hemorrhages, sites of marked narrowing or complete occlusion, thrombi, or ruptured atheromatous abscesses were observed. No atheromatous changes were found within the intima of the renal blood vessels. The intima of the aorta in the thoracic portion showed a small number of atheromatous streaks and plaques, none of which exhibited ulceration or calcification. A moderate number of similar lesions was noted in the abdominal aorta. There was more marked atheromatosis of the pulmonary artery.

Despite the postmortem finding of a remnant of thyroid (1.5 by 1 by 0.8 cm.) beneath the musculature on the body of the thyroid cartilage immediately inferior to the left superior horn, this patient had definite hypothyroidism with elevated serum cholesterol levels for seven years. The thyroid acini were lined by cuboidal to flattened epithelium and contained colloid. There was no suggestion of hyperplasia or adenoma formation.

Case III.* G. F. This male patient, age sixty-three, had had rheumatic fever at the age of twelve years. He had been quite well until three years prior to operation when he experienced precordial pain and dyspnea on effort which became progressively more severe and incapacitating. During the two years before total thyroidectomy he was invalided and showed edema of the legs and sacrum, congestion of the lungs and liver and venous distention despite bed rest, diuretics and the usual medical measures. Physical examination after complete rest in bed for many months showed orthopnea, cyanosis of the lips and mucous membranes, marked enlargement of the heart, grossly irregular heart sounds and a mid-diastolic murmur over the mitral area. There was no aortic diastolic murmur.

Total thyroidectomy was performed December 15, 1932, following which the patient showed a striking response, was employed for ten years as a laboratory assistant and survived until September 4, 1943. During the final ten months of life congestive failure reappeared with attacks of pulmonary edema, one of which proved fatal.

On examination of the heart the coronary arteries were normal except for a minimal area of narrowing and sclerosis at the bifurcation of the left coronary artery into the left circumflex and left anterior descending branch. There was another similar area of narrowing and sclerosis in the left anterior descending branch, 4 cm. from the origin of the left circumflex artery. The mitral valves showed evidence of healed old rheumatic valvulitis. The tricuspid valve showed normal leaflets. Some of the chordae tendinae of the mitral valve were short and thickened. There was marked atherosclerosis of the pulmonary artery and also of the aorta. Careful dissection of the neck revealed no evidence of residual thyroid tissue.

It is noteworthy that this patient in definite myxedema for eleven years showed only minimal changes in the coronary arteries even though there was marked extensive atherosclerosis of the pulmonary artery and systemic aorta.

Case IV. F. Z. This patient, a male, age twenty-two, who survived one year after total thyroidectomy was performed September 14, 1933, showed normal coronary arteries at postmortem examination. The patient had had rheumatic fever at ten years of age. During the two years before first entry to the Beth Israel Hospital he experienced progressively severe dyspnea on exertion, palpitation and attacks of paroxysmal nocturnal dyspnea. Physical examination showed a greatly enlarged heart, the evidences of free aortic insufficiency with blood pressure of 180–300/0, the signs of mitral stenosis and insufficiency and moderate congestive failure. Following total thyroidectomy the patient experienced relief of symptoms for approximately eight months. There was clear clinical evidence of hypothyroidism with a lowered metabolic rate on a regimen of 15 mg. of thyroid daily. Congestive failure recurred, however, and became severe. He died approximately one year following operation.

Postmortem examination disclosed considerable atheromatous change of the aortic intima but no calcification or ulceration. The coronary arteries were not palpable and showed no atheromatosis. In the postmortem protocol of the neck organs it is stated that "there is a chain of smooth moist and glistening reddish purple bodies which strongly resemble thyroid tissue residual from thyroidectomy." It is also stated that "this thyroid-like tissue apparently invests the right recurrent laryngeal nerve which is intimately incorporated with it"; no microscopic observations are available.

* This case is presented in greater detail elsewhere (Case 3).[3]

CASE V. H. G., a male, age twenty-eight years, survived six years in the hypometabolic state after total thyroidectomy August 26, 1933. Five years before operation he noted the onset of dyspnea, palpitation on exertion and swelling of the ankles, legs and hands. Several episodes of hemoptysis had occurred. Physical examination showed cyanosis, the characteristic signs of mitral stenosis and insufficiency, auricular fibrillation, and congestion of the lungs, liver and edema of the legs. The blood pressure was 100/55. The patient showed clinical improvement for approximately six months. While not as severely ill as formerly, he suffered recurrent congestive failure from time to time. The patient was maintained at a clearly myxedematous level during six years, showed marked hypercholesterolemia and received small daily doses of thyroid for only one year. (Table I.) He died in congestive failure with signs of pulmonary embolism and bronchopneumonia on May 7, 1939.

Postmortem examination disclosed a typical fish-mouth appearance of the mitral valve, stenosis of the aortic valve and a greatly hypertrophied heart. After injection and dissection of the coronary vascular tree no sites of narrowing, occlusion or anastomoses were found. There were several irregular patches of moderate atheromatosis scattered along the main coronary arteries.

Throughout the branches of the pulmonary artery to the radicles of the second branching the intima was studded with numerous small, firm, yellowish atheromatous plaques. The thoracic aorta was similarly diffusely studded and a few small atheromatous plaques were observed. None of these was ulcerated or calcified. Nineteen sections of the heart were examined microscopically. Several cross sections of the coronary arteries showed fibrous patchy thickening of the intimal surfaces. In others the intima was atheromatous and sclerotic with compression of the media.

CASE VI. P. R. This female patient, age forty-four, with rheumatic heart disease and severe congestive failure was operated on in 1934 at the Peter Bent Brigham Hospital. She had had repeated hospital admissions for pulmonary infarcts and congestive heart failure. On examination the characteristic murmurs of mitral stenosis and insufficiency and auricular fibrillation were noted. The blood pressure was 130/90. Following operation, symptoms were ameliorated for two years followed by recurrence of severe congestive failure.

This patient had definite clinical myxedema for four years. However, at postmortem examination the coronary arteries were smooth and free of atheromatous change. The aorta, pulmonary, renal and peripheral vessels showed a few small atheromatous plaques and some intimal thickening.

CASE VII. M. A., a forty-six year old woman, survived seven years in the hypothyroid state after total thyroidectomy April 25, 1934. Rheumatic heart disease with mitral stenosis and insufficiency was diagnosed twenty-four years before operation. In the eight years prior to thyroidectomy, dyspnea and palpitation increased and resulted in incapacitation. The blood pressure averaged 166/76. At the time of operation at the Peter Bent Brigham Hospital examination revealed an enlarged heart, auricular fibrillation, basal rales and the characteristic murmurs of mitral stenosis and insufficiency. For two years following thyroidectomy the patient showed clinical improvement; thereafter, the symptoms of congestive failure recurred. Increasing dyspnea, orthopnea and edema precipitated a final hospital admission. Death occurred on October 30, 1941, following a period of shock and a massive pulmonary embolus.

Postmortem examination revealed an enlarged heart, auricular thrombi and marked mitral stenosis. The coronary vessels showed no evidence of thrombi, narrowing or obstruction. A few small atheromatous patches were observed. The vessels of the lung showed unusually extensive atherosclerosis throughout all of the vessels even to the smaller branches. The aorta was elastic and showed no undue tortuosity. Atheromas were few and small in the thoracic aorta but were more numerous without ulceration in the abdominal aorta.

CASE VIII. A. P. This male patient, age fifty-eight, with rheumatic heart disease had suffered increasing dyspnea on exertion for seven years. One year prior to operation marked increase in dyspnea, orthopnea, paroxysmal nocturnal dyspnea and edema resulted in incapacitation. Physical examination at the Peter Bent Brigham Hospital revealed cyanosis, basal rales, hepatomegaly, cardiac enlargement, auricular fibrillation, apical systolic and diastolic murmurs. The blood pressure was 120/96. Total thyroidectomy was performed on February 12, 1934. Improve-

ment in congestive failure for several years was followed by a gradual recurrence of symptoms. The patient showed clear-cut clinical evidence of myxedema during the thirteen years of his survival during which he received small doses of thyroid. He died on May 20, 1947.

Postmortem examination revealed cardiac enlargement, mitral and aortic stenosis and insufficiency. Despite thirteen years of undoubted myxedema the coronary arteries showed no tortuosity, were soft and yielding and showed only slight atheromatous change and no narrowing or occlusions. Moderate atherosclerosis of the pulmonary vessels and of the aorta was found. The renal, peripheral and cerebral vessels were not remarkable. Microscopic examination revealed a small focus of thyroid tissue.

RESULTS

These eight cases represent all those available for study in the entire series of patients at the Beth Israel Hospital and Peter Bent Brigham Hospital* in whom total thyroidectomy was done for the relief of intractable congestive failure due to rheumatic heart disease or cor pulmonale, and in whom hypothyroidism existed one or more years after operation. One other patient, a thirty-two year old female with congenital heart disease, was not included in this series. This patient, following total thyroidectomy, moved to another city, was definitely hypothyroid clinically for many years, and showed no atheromatosis of the coronary arteries at postmortem examination. No blood cholesterol values or basal metabolic rate readings are available, however. No patient with angina pectoris due to arteriosclerotic heart disease was included; narrowing and occlusions of the coronary arteries are commonly present in such patients in the absence of hypometabolism and hypercholesterolemia.[5,7]

Seven of the eight patients had rheumatic heart disease, one patient had cor pulmonale. Their age ranged from twenty-two to sixty-three years, averaging forty-four years, and in six instances exceeded forty years. Five were males, three females. None of the patients had essential hypertension or diseases such as diabetes mellitus, renal or liver diseases, which predispose to atherosclerosis. The average duration of hypothyroidism was 7.4 years; in six of the eight this amounted to six to thirteen years. These patients were definitely hypothyroid clinically and were generally maintained at levels of hypothyroidism corresponding to basal metabolic rates of approximately minus 20 per cent by small doses of thyroid. The blood cholesterol levels of our group averaged 125 mg. above the average pretreatment levels of 170 mg. per cent. Cholesterol values of over 400 mg. per cent were present for many months in some of these patients.

Our observations do not lend support to the oft-repeated statement that hypothyroidism or myxedema with its attendant hypercholesterolemia leads to atheromatosis, particularly of the coronary arteries. In the group of cases reported here the degree of involvement of the coronary arteries was certainly no greater and probably less than that generally witnessed in similar euthyroid individuals with the same disease process. None of the eight cases showed complete occlusions of any of the coronary arteries. Five of the eight cases showed no narrowing of any of the coronary arteries either of the main stems or branches; the other three of the eight showed slight narrowing of one of the main stems. Three of the eight showed no atheromas, and in four additional cases only a few isolated atheromatous areas were witnessed. In but one case was a moderate number of such areas present.

In the other arteries, atheromatosis and atherosclerosis varied greatly but in no instance did it differ from the findings generally observed in similar patients of the same age group who are euthyroid. In three patients (Cases III, VII, VIII), atherosclerotic lesions were observed in the pulmonary and other arteries but did not differ from findings in similar patients without myxedema. The brain was examined in six of the cases; five showed no cerebral atheromatosis; in one patient, a man of sixty-three, slight atherosclerosis was present.

In three of the cases (i.e., Cases I, II and possibly IV) minute thyroid remnants were found which, however, were not sufficient to prevent the hypothyroid state. This is in accordance with our experience with radioactive iodine; certain patients with marked clinical hypothyroidism may nevertheless show the presence of residual thyroid tissue as indicated by radioactive iodine tracer doses.[13,14] We have also observed residual groups of thyroid follicles at postmortem examination in patients who showed

* The cases of the Peter Bent Brigham Hospital were studied through the courtesy of Dr. George W. Thorn and Dr. Samuel A. Levine.

hypercholesterolemia and marked clinical myxedema after I^{131} therapy.

In none of our cases, including over eighty patients treated by total thyroidectomy and over seventy patients rendered hypothyroid by radioactive iodine, have we observed a single case with clinical or pathologic evidence of rupture of the aorta or the degenerative changes described by Kountz[15] and by Foster and Barr.[16] Kountz reported idiopathic cystic medial degeneration of the aorta and other blood vessels after total thyroidectomy and also in patients with low metabolic rates. Rupture of the aorta occurred in three and rupture of a coronary artery in one patient. Foster and Barr reported a case of spontaneous myxedema with degenerative lesions in the cardiac, smooth and skeletal muscles similar to those described by Erdheim as idiopathic cystic medial necrosis. The fact that practically all of our patients are maintained on small doses of thyroid may be partly responsible for the absence of such lesions in our experience.

COMMENTS

It is of interest that the results of our study are in accordance with the original classic report published in 1888[17] of the Committee of the Clinical Society of London to investigate the subject of myxedema. At that time, before any effective treatment of myxedema was known, pathologic examination of the arteries of some twenty cases was summarized as follows: "In more than half the cases there was atheroma of the large arteries, but in only rare instances was the condition advanced. Arterial degeneration, indeed, does not appear to exist to any unusual extent, at any rate in the larger vessels." The clinical summaries of 209 cases reviewed by the Committee indicated that, whatever, the dire effects of myxedema, they were not sufficiently severe to preclude prolonged duration of life. Thus nine cases (Nos. 7, 12, 27, 35, 41, 43, 65, 75, 101) had shown evidences of myxedema for fifteen to thirty-five years at the time that the clinical study was made. The ages of these patients (63, 50, 48, 40, 36, 56, 44, 56, 56) averaged 50 years.

Since then observers have referred frequently to an increased incidence of atherosclerosis accompanying the hypercholesterolemia of hypothyroid states.[18–20] Many of the cases cited in the literature as evidence of a relation of myxedema and atherosclerosis have been complicated by the presence of hypertension[21] or renal disease,[22,23] conditions which in themselves influence the incidence of vascular disease. Moreover, myxedema has its highest incidence at ages when the occurrence of arteriosclerosis without myxedema is common.[22,24,28] Under such circumstances it is uncertain whether arteriosclerosis can be accurately attributed to myxedema alone.[25]

The finding of a high incidence of atherosclerosis in young patients with thyroid deficiency (cretinism, juvenile myxedema) would offer more substantial support of a relation between the two conditions. Although reports do indeed describe extensive atherosclerosis in young athyreotic patients,[26,27] such findings are by no means universal.[28] It is of further interest that atheromas of the aorta have been noted in this group in the presence of apparently normal coronary arteries.[29] On the other hand, Niepce[30] in a classic monograph on cretinism citing postmortem examinations failed to mention atherosclerosis. Similarly, numerous other individual case reports do not describe atherosclerosis.[31–33] Most notable probably is the report of MacCallum and Fabyan[34] of a thirteen year old female "myxedematous idiot" whose coronary arteries were described as "delicate" and whose aorta was normal and quite elastic.

Since, therefore, the coincidence of early atherosclerosis and thyroid insufficiency is irregular, it is an unwarranted extension of the evidence to assume that a primary fundamental or causal relationship always exists between the two conditions. Rather, some other factor, as yet unknown, present only sporadically in cretins and myxedematous patients, may be responsible for atherosclerosis in those particular cases in which it occurs early. A search for such a factor, or for the agent responsible for the absence of atherosclerosis in other young athyreotic patients, might be a fruitful line of investigation.

Whether in myxedema other alterations in the lipid metabolism such as increase in the phospholipids, alterations in the macromolecular lipids[36] or other circumstances offset the possible potentially injurious effects of hypothyroidism cannot be definitely stated. Studies are in progress to elucidate this and related questions.

SUMMARY AND CONCLUSIONS

1. The clinical and postmortem findings are reported in a group of eight patients with

rheumatic heart disease or cor pulmonale, in whom hypothyroidism or myxedema and increase in the cholesterol values was present and who survived one to thirteen years (average 7.4 years) following surgical total thyroidectomy.

2. These patients were definitely hypothyroid clinically, were maintained at levels of hypothyroidism of approximately minus 20 per cent, and showed an average increase in the blood cholesterol level of 125 mg. above the pretreatment levels.

3. None of the eight cases showed complete occlusion of any of the coronary arteries. Five of the eight showed no narrowing of any of the main stems or branches of the coronary arteries. Only three of the eight showed slight narrowing of one of the main stems.

4. In the other arteries atheromatosis and atherosclerosis varied greatly but were similar to that generally observed in similar euthyroid patients.

5. Our results do not, of course, disprove a role of cholesterol in the production of atherosclerosis. These results do demonstrate, however, that over the observed period of time the hypothyroid state with its hypercholesterolemia is not necessarily and by itself a sufficient etiologic factor for the production of coronary atherosclerosis.

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Failure of Ingestion of Cream to Affect Blood Coagulation*

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IN Norway, Strøm and Adelsten Jensen,[1] and Dedichen et al.[2] have reported a decrease in the incidence of postoperative thromboembolic complications and in deaths from circulatory diseases occurring during the years 1940 to 1945. These authors postulated that this reduction was related to a lowered food consumption. Fat intake was most drastically reduced. Evidence that oral administration of fat is followed by an acceleration of the blood clotting time has been reported by Duncan and Waldron[3] and Waldron et al.[4,5] Due to the possible clinical significance of these observations and to the fact that preliminary studies by Schneider and Foley[6] failed to confirm the findings of Duncan and Waldron, it was decided to investigate this problem more thoroughly.

EXPERIMENTAL AND RESULTS

The technic described by Waldron et al.[4] was followed throughout this investigation except that initially only unused sterile glass syringes were used to obtain each blood sample for the clotting time determinations. Waldron's practice of reusing one syringe throughout each complete experiment was thereafter compared with the use of an unused† sterile glass syringe at each venepuncture. Six ward patients, four outpatients, six members of the staff and fifteen medical students were used for these studies. The ward patients were studied under basal conditions. The remaining individuals were moderately active prior to and throughout each experiment. It was found that varying degrees of moderate activity or rest had no effect on the results obtained.

There was no reason to suspect a derangement of the blood clotting mechanism in any subject.

The method for determining the clotting time was as follows: A venepuncture was performed using a glass syringe fitted with a 20-gauge needle, both of which had been rinsed in sterile saline. Blood was withdrawn at a uniform rate and free of air bubbles. The stopwatch was started as soon as blood entered the syringe. The sample was not used if any difficulty was encountered in entering the vein or in withdrawing the blood. One ml. of blood was added to *each* of two collodion (U.S.P. XIV) coated test tubes or to two lusteroid test tubes, with an outside diameter of 13 mm., previously placed in a waterbath at 37°C. Beginning three minutes after the blood was obtained, the first tube was tilted very gently on each occasion to an angle of about 45 degrees until clotting occurred. The second tube was then tilted in the same manner every half minute until clotting occurred. For the purposes of this test coagulation was considered complete when the tube could be held horizontally and the surface of clotted blood remained perpendicular to the sides of the tube. The time required for this to take place in the second tube was recorded as the clotting time. The average normal clotting time in collodion coated test tubes was thirty-five minutes, with a range of twenty-five to forty-five minutes.

Following the criteria of Waldron, et al.[4] we have considered a shortening of the clotting time of 30 per cent or more when compared with the control clotting time as a significant reduction. Any change of lesser degree was considered to be within the normal range of biological and experimental variation.

Part I. Blood samples were drawn before and one-half, one and three hours after the in-

† The term "unused" when applied to a syringe indicates that *before use each time* the syringe has been cleaned and sterilized by heat. The term reused when applied to a syringe indicates that after it has been used for one venepuncture in the experiment it is washed in water and saline before the next venepuncture and is not treated in any other way.

* From the Department of Medicine of the Cornell University Medical College and The New York Hospital, New York, N. Y. Aided by grants from the Kress, Lasker, Hyde and Hampil Foundations.

gestion of cream. In eleven experiments 66 ml. of cream containing 18 per cent fat was administered, and in one experiment 66 ml. of cream containing 36 per cent fat. The clotting time of 100 per cent, 60 per cent and 30 per cent blood was determined on each sample. A previously unused 10 ml. syringe was used for each venepuncture and 9 ml. of blood was withdrawn. One ml. of blood was added to each of 2 lusteroid tubes in the waterbath at 37°c. The dilutions were made by adding 3 ml. of blood to each of two lusteroid tubes containing 2 ml. and 7 ml. of saline solution (0.85 per cent), respectively. Using a 1 ml. glass pipette, 1 ml. of each dilution was transferred to each of two lusteroid tubes in the waterbath.

Results: No significant variation in the clotting time after the ingestion of cream was detected in eleven of the twelve experiments. A significant reduction in clotting time was observed with whole blood, and blood diluted to 60 per cent in only one experiment. No reduction occurred when the test was repeated on this subject. The one experiment in which 36 per cent cream was used differed in no respect from those in which 18 per cent cream was used.

Part II. Blood samples were obtained in three syringes at each venepuncture. The syringes were interchanged on the needle and only one puncture was performed each time. A 10 ml. syringe was used first and then two 5 ml. syringes. These two 5 ml. syringes were reused throughout each experiment, and after each venepuncture were washed in cold running water, rinsed six times in saline solution and, finally, in sterile saline solution. Nine ml. of blood was obtained in the 10 ml. syringe and 1 ml. was transferred to each of six collodion-coated tubes, providing three pairs of tubes with which to determine the clotting time. In the first 5 ml. syringe, 5 ml. of blood was drawn, and 1 ml. was transferred to each of two collodion-coated tubes and two lusteroid tubes. In the second 5 ml. syringe, 3 ml. of blood was drawn and 1 ml. was added to each of two collodion-coated tubes. Ten experiments were conducted. Blood samples were obtained before, and one-half, one, two, three and four hours after the ingestion of 66 ml. of 18 per cent cream.

Results: When the unused sterile syringes were used for each venepuncture, no significant reduction in clotting time was observed after the ingestion of cream in any of the ten experiments except on one occasion when a poor venepuncture had been performed. A significant reduction in clotting time was observed in all cases in which the syringes were reused throughout the experiment and the clotting times were done in collodion-coated tubes. The shortening of the clotting time occurred in blood drawn with both reused 5 ml. syringes in all 10 cases, but the maximum shortening did not occur simultaneously with the two syringes. When the clotting times were done in lusteroid tubes, a similar shortening was observed in all but one case, in which a reduction in clotting time did occur but was not of a sufficient degree to be classed as significant. In the majority of cases the shortening of the clotting time developed within an hour and this usually persisted throughout the remainder of the experiments. However, in a few instances there was a subsequent slight rise toward the control value.

TABLE I

COMPARISON OF THE BLOOD CLOTTING TIMES BEFORE AND AFTER THE ORAL ADMINISTRATION OF CREAM USING UNUSED AND REUSED SYRINGES

Subjects	Previously Unused Syringes (Hours)						Reused Syringes (Hours)					
	0	½	1	2	3	4	0	½	1	2	3	4
C. K.	35	30	29	29	28	35	30	19	24	26	14	33
F. S.	36	31	36	40	39	41	38	26	28	24	26	28
R. E.	38	31	30	30	32	31	36	17	15	14	9	14
T. E.	34	33	30	28*	32	34	37	30	20	12*	20	22
M. K.	39	32	37	32	29	36	47	36	17	32	30	30
M. R.	39	35	36	27	28	36	39	35	33	26	26	34
N. K.	41	46	39	35	41	39	39	21	20	29	23	23
D. M.	37	41	36	35	33	32	40	32	23	28	21	15
S. B.	45	42	43	39	42	39	47	44	33	32	33	32
O. H.	35	34	32	27	32	30	31	30	23	21	23	26

* Poor venepuncture.

Part III. Ten experiments were performed differing in detail only from those described in Part II. The order of use of the syringes was changed, and lusteroid tubes were not used for the clotting time determinations. The two 5 ml. syringes were used first, and 3 ml. of blood was obtained in each for the determination of the clotting time in collodion-coated tubes. The first sample of blood was obtained in a syringe which was reused throughout the experiment, being cleaned after use each time as described in detail in Part II. The second sample was

obtained each time in a sterile unused 5 ml. syringe previously rinsed in sterile saline solution. The 10 ml. syringe was reused throughout each experiment.

Results: In nine of ten cases no significant reduction in clotting time occurred after the ingestion of cream when blood was drawn in previously unused 5 ml. syringes. One subject showed a reduction in clotting time of 30 per cent in two hours. A significant reduction did occur in all ten cases when the syringes were reused throughout each experiment. (Table I and Fig. 1.)

Part IV. Experiments similar to those described in Part III were conducted on ten subjects who fasted throughout the entire experiment. In three of these experiments a fibrinogen solution (500 mg. of Armour bovine fibrinogen dissolved in 100 ml. of 0.85 per cent sodium chloride solution and filtered) was drawn into the syringes at the end of the experiment, as described in Part V. Two experiments were done on subjects who had eaten breakfast and in these the syringes used for the final venepuncture were previously unused.

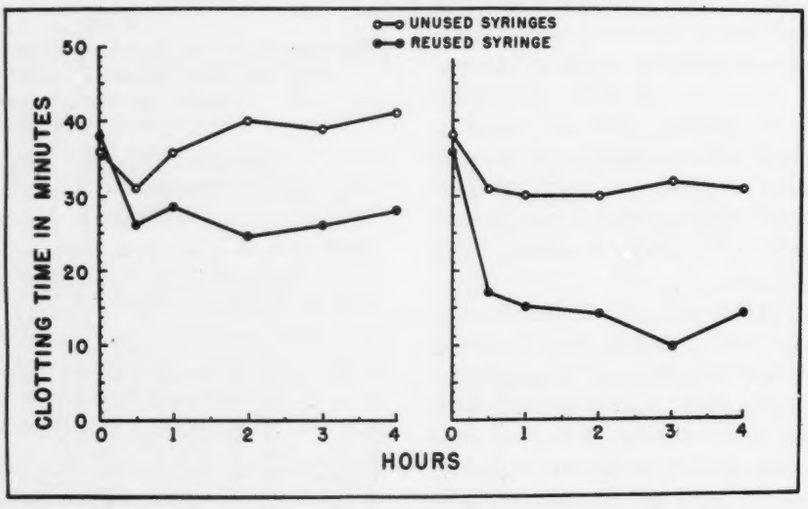

FIG. 1. Blood clotting times before and after oral administration of 66 ml. cream.

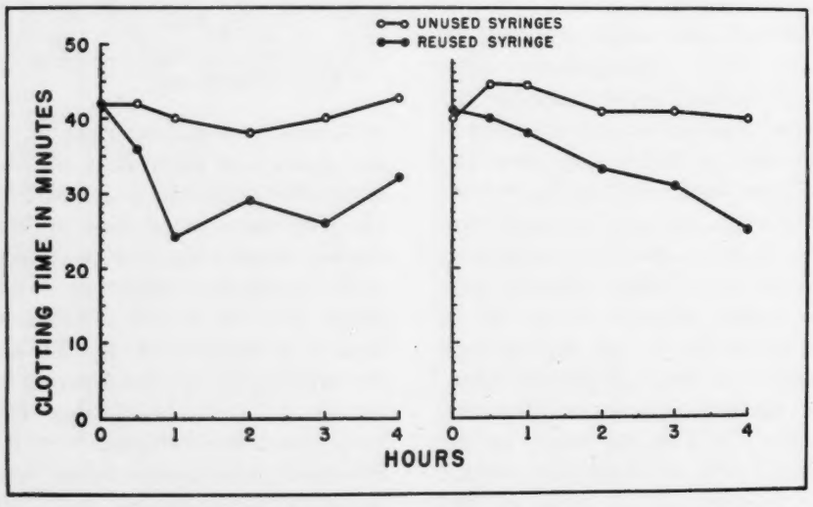

FIG. 2. Blood clotting times in fasting subjects.

Results: No significant variation was observed in nine experiments in which the syringes were used for only one venepuncture. One experiment of ten showed a significant reduction in clotting time. This determination was associated with a faulty venepuncture. A significant reduction in clotting time did occur in nine experiments in which the one syringe was reused six times. (Fig. 2.) No significant variation was

detected in one experiment. In the three cases in which the fibrinogen solution was drawn into the syringes at the end of the experiment, clotting of the fibrinogen occurred in each syringe used six times but not in the syringes used once only. When a reused syringe was used, a significant reduction in the clotting time was observed in the two subjects who had eaten breakfast. A normal clotting time was obtained in these two subjects when previously unused syringes were used for the final venepuncture.

Part V. The effects of employing an unused syringe and a reused syringe were further compared in one experiment. Two 5 ml. syringes were used for each venepuncture. The first was reused throughout the experiment while the second was used once only, a different syringe being used for each venepuncture. The clotting time and prothrombin time were determined initially and at one and two hours. Two venepunctures were done at these intervals. After the final venepuncture the syringes used once and six times were cleaned and the fibrinogen solution drawn into them. One ml. of the fibrinogen solution was transferred from each syringe to each of two collodion-coated test tubes in the waterbath, and the remaining 3 ml. of solution was retained in the syringes. The tubes and syringes were examined at intervals for evidence of clotting of the fibrinogen.

Results: A significant shortening of the clotting time was observed, but there was no change in the prothrombin time when a reused syringe was used. The fibrinogen solution which was drawn into the syringe used six times clotted firmly in forty minutes, and the samples transferred to the collodion-coated test tubes from this syringe clotted in fifty-three minutes. In the syringe used once only a few fibrin strands formed in two hours and fifty minutes and a more definite clot formed in five hours. The samples in the test tubes from this syringe did not clot until the tubes had stood overnight. Clotting also occurred in this stock solution of fibrinogen on standing overnight.

Part VI. The effect of contact with reused glass syringes on a fibrinogen solution was investigated in nine experiments. Six 5 ml. syringes were used in each experiment and blood samples were obtained initially and one-half, one, two, three and four hours thereafter. Three ml. of blood was drawn in each syringe for the clotting time determination in collodion-coated test tubes. After each venepuncture the syringes were cleaned as described in Part II, and one of the syringes was placed aside. At the end of this part of the experiment the six syringes had been used one, two, three, four, five and six times, respectively. The fibrinogen solution was then drawn into each syringe and also, for control purposes, into a seventh syringe which had only been rinsed in sterile saline. One ml. of the fibrinogen solution was immediately transferred from each syringe to each of two collodion-coated test tubes in the waterbath and the remainder was retained in the syringes. In one experiment the syringe used five times was heated to 100°C. for sixty minutes and allowed to cool before it was filled with the fibrinogen solution. In five experiments a silicone-coated syringe was added to the series and was used five times in each experiment.

TABLE II
INCIDENCE OF CLOTTING OF A FIBRINOGEN SOLUTION IN CONTACT WITH REUSED GLASS SYRINGES

No. of Times Syringes Used	Subjects								
	1	2	3	4	5	6	7	8	9
0 (Control)	..	..	..	..	..	..	..	..	..
1	..	..	..	..	..	..	..	..	..
2	..	..	C	..	..	..	..	..	..
3	C	C	C	..	..	..	..	C	C
4	C	C	C	C	..	C	C	C	C
5	..	C	C	..*	..	C	..	C	C
5 (Silicone-coated)	..	..	..	..	..	..	..	small clot	..
6	..	C	C	C	C	C	..	C	C

C = Clot.
* Syringe heated to 100°C. for 60 minutes.

Results: In the first four experiments the syringe used first at each venepuncture was placed aside each time. It was noticed that the clotting time of the blood samples obtained in the last syringe at each venepuncture was significantly shorter than the clotting time of blood obtained in the first syringe. Due to this observation it was considered advisable to reverse the order in which the syringes were placed aside. The last syringe used at each venepuncture was therefore set aside each time. The clotting times of successive blood samples obtained with the same syringe are therefore comparable in the five experiments conducted following the latter procedure. In these five experiments there was a definite reduction in the

clotting times obtained with the syringes used six times, and in four experiments with the syringes used five and four times, respectively, although with the latter syringe two of the short clotting times were obtained after a poor venepuncture or after difficulty with the interchange of syringes on the needle. No significant reduction in clotting time was observed with syringes used less than four times. When the siliconized syringe was used five times no significant variation in clotting time was observed.

TABLE III
INCIDENCE OF CLOTTING OF A FIBRINOGEN SOLUTION IN COLLODION-COATED TEST TUBES FILLED FROM REUSED SYRINGES

No. of Times Syringes Used	Subjects								
	1	2	3	4	5	6	7	8	9
0 (Control)	..	..	..	..	..	..	..	..	..
1	..	..	..	..	..	..	..	..	..
2	..	..	..	..	..	..	..	..	..
3	..	..	C	..	..	..	..	..	C
4	..	C	C	C	..	C	C	..	C
5	..	C	C	..*	..	C	..	C	C
5 (Silicone-coated)	..	..	..	..	..	..	..	..	..
6	..	..	C	..	C	C	..	C	C

C = Clot.
* Syringe heated to 100°C. for 60 minutes.

TABLE IV
INCIDENCE OF CLOTTING OF A FIBRINOGEN SOLUTION IN REUSED GLASS SYRINGES AND IN SAMPLES TRANSFERRED TO COLLODION-COATED TEST TUBES

No. of Times Syringes Used	Dicumarol		No Dicumarol	
	Syringes	Test Tubes	Syringes	Test Tubes
0 (control)	..	..	..	..
1	..	..	..	..
2	..	..	C	C
3	..	..	C	C
4	C (trace)	..	C	C
5	..	..	C	C
6	..	..	C	C

C = Clot.

The results obtained when a fibrinogen solution was drawn into the syringes after use, and also into the unused control syringe are shown in Tables II and III.

Part VII. Two experiments as described in Part VI were conducted on one subject, the first while he was receiving dicumarol, and the second one month after he had discontinued this treatment.

Results: In the first experiment on this subject the serial clotting times are not comparable, for reasons stated in Part VI. A definite reduction in clotting time was observed in the second experiment with the syringes used four, five and six times. The control clotting time obtained in the second experiment was shorter than any clotting time obtained during the first experiment while the subject was taking dicumarol. The prothrombin time was 21.6 seconds, control 14.6 seconds, at the time of the first experiment, and was normal at the second test. When the fibrinogen solution was drawn into the syringes at the end of each experiment, a soft clot formed after thirteen hours in only one syringe used during the first experiment, but in the second experiment clotting appeared rapidly in the syringes used two, three, four, five and six times. (Table IV.)

COMMENTS

The initial observations reported in Part I provided no evidence of any shortening of the clotting time during the three-hour period following the ingestion of cream. These results did not confirm the reports by Duncan and Waldron[3] and Waldron et al.[4,5] This unexplained discrepancy could be due to possible differences in technic. When observing the technic of the test as performed by Waldron, only one difference was noted, namely, that it was his practice to use one syringe throughout the experiment, washing it in water and saline solution after use each time. This technic was incorporated in our experiments, and the clotting time of blood drawn in a series of unused sterile syringes was compared with that of blood drawn in a single reused syringe. Blood drawn in reused glass syringes clotted more quickly than blood drawn in previously unused glass syringes. The shortening generally became of a significant degree after the syringe had been reused twice. Repeated venepunctures using an unused sterile syringe each time did not appreciably alter the clotting time during a three- or four-hour period. These observations held true whether the subject had taken cream,

was fasting or had eaten breakfast. The reason for this discrepancy between the results with the two syringes was therefore investigated.

The prothrombin time was not altered in the blood drawn with the reused syringe; however, the clotting time was shortened. This suggested that the factor accelerating the clotting time possessed insufficient activity to influence the prothrombin time. Since thrombin is known to adhere to glass surfaces,[7–9] the possibility that the observations of Waldron could be explained on this basis was investigated. The presence of thrombin activity on the surface of reused glass syringes was demonstrated by the following experiments:

1. Reused glass syringes were filled with solutions of bovine (Armour) fibrinogen and observed for clotting. As reported in the results of Part V, VI and VII, and illustrated in Tables II and III, clotting of the fibrinogen occurred in practically all of the syringes reused three times or more. No clotting occurred in the syringes used once only except for one case which is reported in Part V. There was some variation from one experiment to the next in the amount of fibrin formed and in the time required for clot formation. This would suggest that the adhesiveness of thrombin to glass varies, depending possibly on the nature of the surface. The effectiveness of thrombin activity in clotting fibrinogen is also shown by the frequency with which clotting occurred in the test tubes filled from the reused glass syringes even though the period of contact of the fibrinogen and glass surface had been less than thirty seconds.

2. In five experiments a silicone-coated syringe, reused five times, was employed. In none of the five experiments did a significant shortening of the clotting time occur, although this did occur in four of these five experiments when a glass syringe was reused five times. A fibrinogen solution drawn into the silicone-coated syringe did not clot except on one occasion when a very soft clot formed. This was noted in the fourth experiment and possibly the syringe was in need of recoating with silicone. On recoating this syringe with silicone no clotting of fibrinogen occurred in the syringe after the fifth experiment. These experiments indicate that thrombin does not adhere to a silicon-coated surface. This observation has previously been noted by Waugh.[10]

3. In one experiment the syringe used five times was heated to 100°C. for sixty minutes and was cooled before the fibrinogen solution was drawn into it. No clot developed in this syringe, although clotting did occur in the syringes used four and six times in this experiment. It is well recognized that thrombin is inactivated by heat.

4. Further evidence of the presence of thrombin activity on the surface of reused glass syringes was provided by comparing experiments done on a patient while he was receiving dicumarol and had a prolonged prothrombin time, and later after he had discontinued the drug and had a normal prothrombin time. In the first experiment when the prothrombin time was prolonged minimal clotting of the fibrinogen solution occurred in one of the reused syringes after thirteen hours. When the prothrombin time was normal, clotting occurred in five reused glass syringes. (Table IV.) The diminution in prothrombin activity present at the time of the first experiment probably interfered with thrombin formation.

These observations establish the presence of thrombin activity on the surface of reused glass syringes. It is therefore difficult to explain the results obtained by Waldron, et al.[4] in their control subjects when no acceleration of clotting time was observed after the oral administration of 60 ml. of water.

In a number of the experiments reported in this paper a tendency was noted for the blood clotting time to return toward the control value after a significant shortening had occurred. (Table I.) This same biphasic type of curve is illustrated in one of Waldron's graphs.[4] A possible explanation of this observation is that after repeated venepunctures using the same syringe the activity of the adsorbed thrombin varies, depending possibly on the glass surface of the syringe or on the inactivation of the adsorbed thrombin by some unknown mechanism.

SUMMARY

1. The blood clotting time is not altered by the oral administration of cream.

2. When one syringe is reused for successive venepunctures, the blood clotting time is accelerated, irrespective of whether the subject has ingested cream, eaten breakfast or is in the fasting state. This is true whether the subject is active or is in a basal state.

3. Evidence of thrombin activity has been demonstrated on the surface of reused glass syringes.

4. The practice of reusing a glass syringe for the determination of the blood clotting time without heat sterilization of the syringe between each venepuncture is inaccurate and should not be used.

5. These findings raise doubt as to whether the ingestion of fat in the form of dairy products affects the incidence of thrombosing conditions by immediate direct action on the clotting mechanism of the blood.

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An Evaluation of Anticoagulant Therapy in Myocardial Infarction Based on Prognostic Categories*

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THE evaluation of anticoagulant therapy in myocardial infarction has received much attention particularly since 1945 when Wright[1] reported his experience with the use of dicumarol® in seventy-six cases of myocardial infarction. During the next five years there were many reports of the use of heparin® and/or dicumarol in myocardial infarction.[2–33] The larger experiences were those of Wright,[4,8,9,12,18] Peters and Brambel,[3,10] Nichol,[2,5,17] Parker and Barker[7,11] and the American Heart Association joint study.[12,19,27] With few exceptions[20,33] these reports indicated that the mortality and thromboembolic complications of the disease could be reduced significantly by the use of anticoagulants. This led to the belief, expressed editorially in 1949[34] and by the American Heart Association joint study committee,[19] that dicumarol (with or without heparin at the onset) should be administered to every patient with myocardial infarction, barring specific contraindication. Enthusiasm for anticoagulants in this disorder led to their use as prophylactic agents, mainly by Nichol[16,17,25,26] and Wright.[35,36]

These developments took place even while an impressive number of episodes of serious bleeding as well as deaths due to hemorrhage were recorded (reports of the latter numbering eighty by 1950[37] and well over one hundred by 1952[38]) and the development of thromboembolic complications in dicumarol-treated patients with "adequate" or "therapeutic" depression of prothrombin concentration was noted.[25,26,39–41] At the same time animal experiments demonstrated that the incidence of experimental intravascular thrombosis in dogs was not significantly reduced by dicumarol-induced hypoprothrombinemia[42] and heparinization of dogs started one hour after coronary ligation and maintained for twenty-four hours had no appreciable effect on the extent of the myocardial infarction found one week later.[43] However, many of the favorable reports came under critical review[44] and some re-evaluation of the prognosis for the patient who has experienced a myocardial infarction was attempted by several authors.[45–52] Critical review emphasized that the outlook for any patient depends on the presence (or absence) of a variety of factors, signs and symptoms. Such factors did not receive adequate consideration in many earlier reports. The findings indicate that the routine use of anticoagulants in all cases in which specific contraindication does not exist may be unnecessary. It has also become evident that there are "serious defects in the claims of the proponents of such therapy"[44] and that future evaluation of these and other anticoagulant agents must be made within the framework of "prognostic categories."[20,46]

Russek and his associates[38,45] devised a more precise analysis of two prognostic categories by establishing criteria to classify patients as "good risks" or "poor risks." Indicative of a

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guarded prognosis were: (1) previous myocardial infarction, (2) intractable pain, (3) extreme degree or persistence of shock, (4) "significant" cardiac enlargement, (5) gallop rhythm, (6) congestive failure, (7) auricular fibrillation or flutter, ventricular tachycardia or intraventricular block and (8) diabetic acidosis, marked obesity, previous pulmonary embolism, lower extremity varicosities, present or past thromboembolic disorder. The presence of one or more of these unfavorable signs or symptoms during the first hospital day indicated that the patient was a "poor risk." There were 335 deaths (60 per cent mortality) and 10.6 per cent incidence of thromboembolic phenomena in 558 subjects in this group. The incidence of theoretically preventable deaths in the "good risk" group was 1 per cent and thromboembolism occurred in only 0.8 per cent. The authors conclude that anticoagulant therapy should be reserved for the "poor risk" group.

MATERIALS AND METHODS

Our study of anticoagulant therapy in myocardial infarction over the past several years has been made within the framework of classification according to prognostic categories.[20,46] The present report is based on a study of 100 attacks of myocardial infarction treated with dicumarol or dicumarol and heparin. An earlier group of 211* patients receiving conventional therapy, but no anticoagulants, serve as controls. All patients were admitted to the Vanderbilt University Hospital. Any patient who died within twenty-four hours following admission to the hospital was excluded from the study unless heparin was given initially. Twenty-one patients received heparin in addition to dicumarol until the prothrombin concentration had reached the therapeutic range of 10 to 30 per cent. Daily prothrombin determinations were carried out utilizing a modified Link-Shapiro technic with undiluted plasma, and dicumarol was administered in doses sufficient to maintain the prothrombin concentration between 10 and 30 per cent. No significant bleeding was encountered. Vitamin K was administered to seven patients whose prothrombin concentrations fell considerably below 10 per cent, but anticoagulant therapy was ultimately resumed. "Mortality" was defined as death within a thirty-day period following the attack. The diagnosis of infarction was made on the basis of one or more of the following findings: (1) typical history with ECG changes characteristic of or compatible with infarction, (2) history compatible with infarction but ECG changes unequivocal and (3) autopsy evidence.

TABLE I
MYOCARDIAL INFARCTION: MORTALITY IN PROGNOSTIC CATEGORIES

	Anticoagulant-treated		Control	
	No.	30-day Mortality	No.	30-day Mortality
Very Poor Risk				
(a) 1st Attack: shock + diabetes and/or azotemia				
(b) History of previous attack: shock; congestive failure + diabetes and azotemia	7	7 (100%)	22	21 (95%)
Poor Risk				
Shock, congestive failure, diabetes or azotemia	43	10 (23%)	113	46 (41%)
Sub-total	50	17 (34%)	135	67 (50%)
Good Risk				
None of the above criteria	50	1 (2%)	76	1 (1%)
Total	100	18 (18%)	211	68 (32%)

RESULTS AND COMMENTS

The mortality for the control group was 32 per cent, for the anticoagulant-treated series 18 per cent. The application of three simple criteria permitted the establishment of "good risk" and "poor risk" groups. (Table I.) The presence of shock, congestive failure, diabetes or azotemia* within the first week of the attack put any patient in the "poor risk" category. Further subdivision of the poor risk category into a "very poor risk" group was possible when any of the following combinations were found: (1) first attack with shock plus diabetes or azotemia, (2) history of previous attack and shock, (3) history of previous attack and congestive failure plus diabetes and azotemia. The absence of such factors as hypertension, arrhythmias, angina and others from the criteria listed above does not imply that their presence is without signifi-

* Those who refer to our earlier publication[46] will note a discrepancy in the total number of the series described therein and the series as used here for control purposes. The difference is due to elimination from the "control series" of those patients who died within twenty-four hours since such patients were not included in the "treated series." This is also the explanation for slightly different per cent mortalities.

* Azotemia is defined as a serum NPN value in excess of 40 mg. per cent.

ance in determining the prognosis in individual cases of myocardial infarction.

Fifty attacks in the treated group were classified as "good risks," an incidence of 50 per cent, which is quite similar to Russek's experience.[38,45] One patient died, a 2 per cent mortality. This patient was a psychotic female who became violent, requiring almost continuous restraint. (Rupture of the interventricular septum occurred.) In the control group, seventy-six subjects qualified as "good risks," (36 per cent incidence) with one death (1.3 per cent mortality). The recovery rate for patients in either "good risk" group was 98 per cent. The difference between the incidence of good risk patients in the treated and control groups emphasizes the need for patient classification on the basis of prognostic categories if a valid comparison is to be made.

Seven patients in the anticoagulant treated series were classified in the "very poor risk" category (an incidence of 7 per cent). All died. Twenty-two of the controls were considered "very poor risks" (an incidence of 10.4 per cent). One of these survived, a 95 per cent mortality. The recovery rate for patients in either "very poor risk" category then did not exceed 2 per cent.

Any form of special therapy would be difficult to evaluate if 98 per cent of the patients could be expected to recover with conventional management. On the other hand, the evaluation of such therapy in a group of patients whose outlook was virtually hopeless would provide a very severe test of its efficacy. While the absolute numbers of patients in this latter category are small in both treated and control groups, there is no evidence that dicumarol or dicumarol and heparin alter the grave prognosis.

TABLE II

POOR RISK ANALYSIS

	Treated Series				Control Series		
	No.	Deaths	Mortality (%)		No.	Deaths	Mortality (%)
First Attack							
Shock	7	1	14	Shock	12	5	42
Congestive failure	17	3	18	Congestive failure	43	16	37
Diabetes and/or azotemia	16	3	19	Diabetes and/or azotemia	52	21	40
Total no. patients	36	7	19	Total no. patients	84	35	42
History of Previous Attack							
Congestive failure	6	2	35	Congestive failure	19	11	58
Diabetes or azotemia	1	1	100	Diabetes or azotemia	29	9	31
Total no. patients	7	3	43	Total no. patients	29	11	38

We are obliged then to turn our attention to the residual or "poor risk" group for an adequate appraisal of anticoagulant therapy. Forty-three patients in the anticoagulant-treated series were considered "poor risks," an incidence of 43 per cent. Ten died, mortality 23 per cent. One hundred thirteen patients in the control series were "poor risks," an incidence of 54 per cent. Forty-six died, a 41 per cent mortality. This 41 per cent mortality is significantly higher ($P < .05$) than the 23 per cent in the same category of the treated series. It would seem that the beneficial effect of anticoagulant therapy is manifest in this "poor risk" group.

The populations of the treated and control "poor risk" groups were examined with regard to age and sex. The mean ages of the treated and control subjects were the same: 61.0 ± 1.5 and 61.6 ± 1.0 years, respectively, and the age distribution curves were similar. The ratio of males to females differed somewhat. In the treated series it was 4:1 while in the controls it was 2:1. The relatively greater number of females in the control series was of little importance since the male and female mortality were substantially the same. Differences between the mortality rates of the anticoagulant-treated and

control "poor risk" groups cannot be ascribed to age or sex factors. The incidence of hypertension was higher in the control series but the mortality in those with hypertension did not differ from the group as a whole.

TABLE III
DISTRIBUTION OF FIRST-ATTACK "POOR RISK" SUBJECTS ACCORDING TO SINGLE OR MULTIPLE EXPOSURE TO RISKS

Risk Exposure	Treated Group			Risk Exposure	Control		
	No.	Deaths	Mortality (%)		No.	Deaths	Mortality (%)
Single	17	1	6	Single	41	17	41
Multiple	19	6	32	Multiple	43	18	42
Total	36	7	19	Total	84	35	42

Analysis of the "poor risk" group classified according to first and previous attacks (Table II) revealed that the greater apparent benefit of anticoagulant therapy is in the first attack group. This is not surprising since previous infarction can be expected to increase cardiac vulnerability to any type of insult. Further scrutiny of the first attack groups was therefore carried out. In this group there were patients who exhibited only one of the three criteria (shock, congestive failure and diabetes and/or azotemia) necessary for inclusion in the first attack, "poor risk" category. If each criterion is looked upon as a risk, the patient who exhibits two or three of these criteria has a greater "risk-exposure" than the subject who exhibits only one. Accordingly, the first attack groups were considered on the basis of single and multiple risk exposures. (Table III.) The incidence of single and multiple risk exposures is similar in both the anticoagulant-treated and control groups. Among the anticoagulant-treated, "poor risk" patients who were experiencing their first attack there were seventeen subjects with a single risk exposure (one died) and nineteen with multiple exposure (six died). In the controls there were forty-one subjects with only a single risk exposure (seventeen died) and forty-three with a multiple exposure (eighteen died). Again, as might be expected, apparent benefit was greatest in those subjects in the "poor risk" category who were experiencing their first attack and who exhibited only one poor prognostic sign.

Now that there may be determined a group of patients who appear to have benefited most from the administration of anticoagulants, attention may be directed to the nature of such benefit. Accordingly, each group of patients was examined for evidences of thromboembolic phenomena. Reasonable clinical evidence of thrombophlebitis, phlebothrombosis or embolization, autopsy evidence of mural thrombus (with or without evidence of embolization), pulmonary, cerebral or other embolization, or localized thrombosis (exclusive of the coronary arteries) were included in the term "thromboembolic phenomena." The incidence of such phenomena is tabulated according to prognostic categories in Table IV. In the series of one hundred treated attacks there was a 14 per cent incidence of thromboembolic phenomena, compared with a 19 per cent incidence in the control series of 211 attacks. There were six deaths in the anticoagulant-treated group which were associated with thromboembolic phenomena (6 per cent) while in the control group there were twenty-nine such deaths (14 per cent).

Since autopsy not infrequently provided the only evidence of thrombosis, it is important to point out that the total incidence of thromboembolism (clinically and at autopsy) in the control series would undoubtedly have been somewhat higher had the autopsy rate in the control group (46 per cent) equaled that of the treated series (77 per cent), i.e., more autopsies, more evidence of thromboembolism. However, the primary objective in the treatment of myocardial infarction is the survival of the patient, not a reduction in the incidence of thrombotic manifestations noted at autopsy. Of the six treated patients who died with (but not necessarily because of) associated thrombotic phenomena, two did not receive "ideal" anticoagu-

lant therapy. These two subjects, however, exhibited only mural thrombi as a thrombotic manifestation. On the other hand, the failure of "ideal" anticoagulant therapy to prevent mural thrombi is evidenced by the presence of mural thrombi in four of these subjects in whom anticoagulant therapy provided satisfactory control of the prothrombin concentration.

The greatest reduction in the incidence of thromboembolic phenomena appeared in the "very poor risk" category. In this category of the control group twelve of the twenty-one patients dying had an associated thromboembolic manifestation while in the anticoagulant-treated group only one of the seven dying had such a manifestation. Inspection of the "poor risk" categories in Table IV wherein patients were subdivided according to the presence or absence of a history of a previous myocardial infarction shows little change in either the incidence of thromboembolic events in the treated group, or the frequency with which such events were associated with death.

The lower mortality noted in the treated groups cannot be explained, except in small measure, by the slight reduction in the incidence of thromboembolic phenomena which presumably was related to the administration of anticoagulants. The value of a reduction in the incidence of thromboembolic phenomena in regard to improving the outlook for life is further questioned, since the group demonstrating the most significant reduction in this regard experienced no improvement in mortality.

While anticoagulants do reduce the incidence of thromboembolic phenomena, in our experience thromboembolic complications have played a minor role in the course of acute myocardial infarction. We are forced to the conclusion, therefore, that the lower mortality rate in these patients treated with anticoagulants was due either to some property of these agents in addition to their anticoagulant property, or to other entirely unrelated and undetected factors. Of interest in relation to the possible existence of some other pharmacologic property of heparin and/or dicumarol are the reports by Gilbert and Nalefski[52] that dicumarol and heparin (the latter to a somewhat lesser degree) will increase the volume of coronary flow in experimental animals. The effect of dicumarol is said to equal that of the xanthines and to be of greater duration. Nichol[26] has reported the relief of angina following the administration of anticoagulants to patients considered to be showing signs of threatened myocardial infarction. Gofman and associates[54] report "dramatic and uniform relief" and Engelberg[55] "the reduction of incidence of attacks" after the administration of heparin to patients with severe angina pectoris. Holten,[56] reporting on the experience with anticoagulants in Denmark, noted that the mortality in 174 anticoagulant-treated cases showed the most marked improvement during the first ten

TABLE IV

INCIDENCE OF THROMBOEMBOLIC PHENOMENA (TE) IN SURVIVORS AND THOSE DYING, ACCORDING TO PROGNOSTIC CATEGORIES

Anticoagulant-treated				Control			
	Surviving	Died	Total		Surviving	Died	Total
Good risks	49	1	50	Good risks	75	1	76
TE	3	1	4 (8%)	TE	3	0	3 (4%)
Poor risk, 1st attack	29	7	36	Poor risk, 1st attack	49	35	84
TE	4	2	6 (17%)	TE	6	12	18 (21%)
Poor risk, previous attacks	4	3	7	Poor risk, previous attacks	18	11	29
TE	1	2	3 (43%)	TE	3	5	8 (28%)
Total poor risk	33	10	43	Total poor risk	67	46	113
TE	5	4	9 (21%)	TE	9	17	26 (23%)
Very poor risk	0	7	7	Very poor risk	1	21	22
TE	0	1	1 (14%)	TE	0	12	12 (55%)
Grand total	82	18	100	Grand total	143	68	211
TE	8	6	14 (14%)	TE	12	29	41 (19%)

days of the attack. The peak incidence of thromboembolism in both his treated and control series was later than the ninth day, suggesting that the apparent benefit noted in the group treated with anticoagulants was not due entirely to the prevention of thromboembolic phenomena.

Other factors make difficult an accurate appraisal of anticoagulant therapy in myocardial infarction. This is especially true when a study covers a several-year period during which time methods of treatment for such complications as pneumonia, shock, diabetes, electrolyte disturbances, congestive failure, etc., may undergo significant revision and improvement. What effect has an ever increasing coverage with hospitalization insurance on the time or rate of hospitalization of patients? How much benefit accrues to the patient who is part of the study of any therapeutic agent, by reason of the extra interest and attention paid him, and how much better would be the outlook for the control subject were he to be favored with as much attention? Many other factors of possible influence come to mind.

This report and other recent studies do not indicate that anticoagulants are not of benefit in myocardial infarction or that they do not prevent thrombosis. That they are beneficial in one particular group of patients with infarction is clear.

It is interesting that replies to a recent questionnaire sent to 228 internists and cardiologists by Russek[38] and his associates revealed that half of them still employ anticoagulants routinely in all cases of myocardial infarction when no contraindications exist. Further appraisals along the lines of Russek's studies and those of the present authors are needed.

SUMMARY

Dicumarol or dicumarol and heparin were administered during one hundred episodes of acute myocardial infarction. An earlier group of 211 patients served as controls.

Patients were sorted into prognostic categories according to the following criteria: (1) *Very poor risks:* (*a*) The attack was the patient's first; shock and diabetes or shock and azotemia were present; (*b*) a previous attack had occurred; shock was present or congestive failure and diabetes and azotemia were present. (2) *Poor risks:* Shock, congestive failure, diabetes or azotemia were present within the first week of admission. (3) *Good risks:* None of the concomitant manifestations in groups 1 and 2 were present.

Anticoagulants failed to improve the mortality in the "very poor risk" category.

The mortality in the "good risk" category was very small with or without anticoagulants.

The beneficial effects of anticoagulants were most apparent in the "poor risk" group of patients and then chiefly so in those less severely ill. Such beneficial effects cannot be entirely ascribed to a reduction in thromboembolic phenomena.

The need for further evaluation of anticoagulant therapy in myocardial infarction within a framework of prognostic categories is emphasized.

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The Control of Prothrombin Activity with Tromexan Therapy*

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DIFFICULTIES in the control of the hypothrombinemic effect of dicumarol® in the treatment of thromboembolic diseases have led to the investigation of other coumarin derivatives. With one of these, tromexan®† (3,3′-carboxymethylenbis [4-hydroxycoumarin] ethyl ester), the therapeutic effects take place more rapidly after administration of the drug and disappear more rapidly after discontinuance of the drug than is the case with dicumarol. These characteristics of tromexan are potential advantages in that they might be expected to permit more predictable control of induced hypoprothrombinemia. There was some confirmation of the early expectations[1–5] but this has not been borne out in later studies.[6,7]

Previous work[8] indicates that tromexan is rapidly and completely absorbed from the gastrointestinal tract, compared to the slow and sometimes incomplete absorption of dicumarol. Its biotransformation is rapid, the plasma concentration falling at an average rate of 25 per cent per hour, compared to dicumarol which falls at an average rate of about 40 per cent per day.[9] As with dicumarol the rate of metabolic transformation of tromexan varies widely in different subjects. The rapid disappearance of tromexan from the body is accompanied with a rapid return of the prothrombin time to pretreatment levels on discontinuing therapy. After a single dose the drug has almost disappeared from the body before the prothrombin response becomes evident, eight to twelve hours after drug administration.‡ Single daily doses of the drug result in detectable plasma concentrations for only a few hours each day but the prothrombin response is cumulative and reaches a plateau after several days of therapy. This basic information has been utilized in an evaluation of the clinical results obtained with tromexan.

METHODS AND MATERIALS

Prothrombin times of whole plasma were determined by the one-stage technic.[11] A single lot of lyophilized thromboplastin preparation was used.§ The activity of this material showed no change during the course of these observations. The average normal value for plasma prothrombin time by this technic was sixteen seconds. A prothrombin time of twenty-five to fifty seconds was arbitrarily set as the objective of tromexan therapy.

Fifty hospitalized patients (twenty-nine males and twenty-one females) aged twenty-five to eighty-two years (average fifty-five years) with prothrombin times between fourteen to eighteen seconds were used in the study. Twenty-five of the patients had cardiac or peripheral thromboembolic disease; the rest were individuals with chronic spastic neurologic disorders.

EXPERIMENTS

Response to a Priming Dose of Tromexan. Ordinarily a large initial "priming" dose of tromexan is administered to bring the prothrombin time within the desired therapeutic range quickly. Then the prolonged prothrombin time is maintained using smaller daily doses.

The response to a priming dose of tromexan generally reaches its maximum in about twenty-

† Tromexan was supplied to us through the courtesy of Geigy Pharmaceuticals, New York, N. Y.

‡ An important route of metabolism is through its oxidation to a hydroxy-derivative which has no anticoagulant activity.[10]

§ Simplastin, supplied by Chilcott Laboratories, Morris Plains, N. J.

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four hours, compared to about seventy-two hours following dicumarol. It would seem, therefore, that it should be possible to achieve a therapeutic prothrombin time level more rapidly with tromexan than with dicumarol. Studies were designed to determine how rapidly, in practice, a therapeutic response could be achieved in subjects on tromexan therapy.

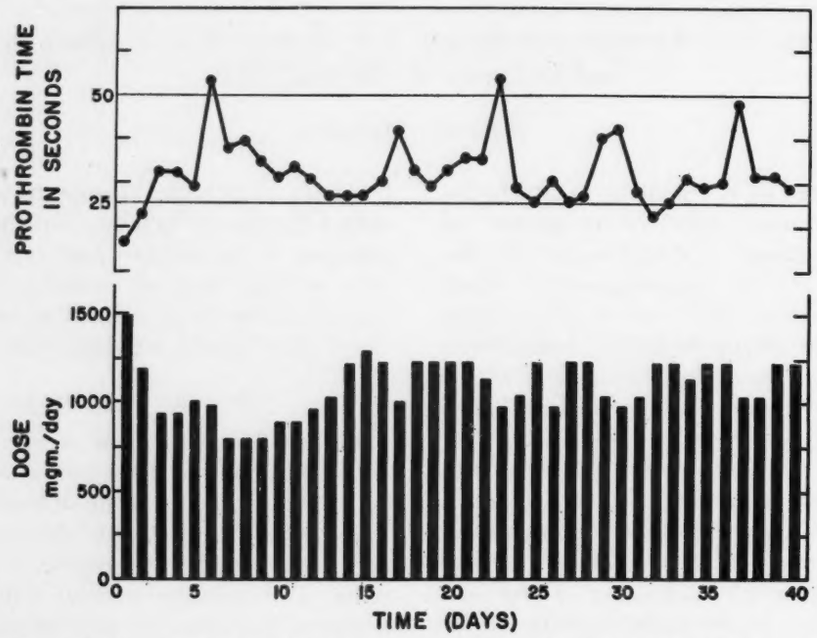

FIG. 1. Patient A. Days 1 to 2: therapeutic level is achieved in forty-eight hours following two large doses of tromexan. Days 3 to 41: adequate prothrombin control maintained by adjustments of large daily doses averaging 1,050 mg./day.

Fifty subjects were given 20 mg. per kg. of tromexan orally in a single dose. Twenty-four hours later thirty-three subjects showed an inadequate response, that is, a prothrombin time below twenty-five seconds, and seventeen showed responses in the therapeutic range of twenty-five to fifty seconds. Four of these seventeen showed a further rise during the next twenty-four hours although no additional drug was given. Two of these four showed an unusual sensitivity to the drug in that their prothrombin times rose above fifty seconds and did not return to the pretreatment level for more than four days.

Twenty-one of the thirty-three subjects who failed to achieve an adequate prothrombin response in twenty-four hours were given additional doses of 1,000 mg. Only ten of these twenty-one were in the therapeutic range in the next twenty-four hours. The remaining eleven subjects were continued on doses of 1,000 mg. daily until their prothrombin times reached the therapeutic range. Four subjects require six or more days of this daily dosage before their prothrombin time rose above twenty-five seconds. From these data it is evident that, in practice, a therapeutic prothrombin level is usually not achieved within twenty-four hours after a priming dose of 20 mg. per kg.

Response to Maintenance Doses of Tromexan. Twenty-seven subjects were given orally a priming dose of 20 mg. per kg. of tromexan followed by daily maintenance doses of the drug for a total of 616 patient-days. The daily dose was regulated according to the concurrent prothrombin time. The second administration of drug usually ranged between 600 and 1,000 mg. The average daily dose required after the first forty-eight hours varied from less than 150 mg. in sensitive subjects to over 1,000 mg. in resistant subjects. Excluding the day of initial dosage, the prothrombin time was outside the desired range for 194 of the 616 patient-days of therapy. The dosage-prothrombin responses of four of these subjects are shown graphically in order to illustrate the observations noted hereinafter.

As a rule the prothrombin times showed considerable daily fluctuations, only a few subjects showing a smooth plateau type of response curve. The prothrombin response in fourteen subjects was kept within the bounds of the arbitrarily set objective of twenty-five to fifty seconds in spite of irregular fluctuations. (Fig. 1.)

The remaining thirteen subjects displayed at one time or another erratic changes in prothrombin time that strayed outside therapeutic limits despite the daily adjustment of dosage. In some instances satisfactory control would be

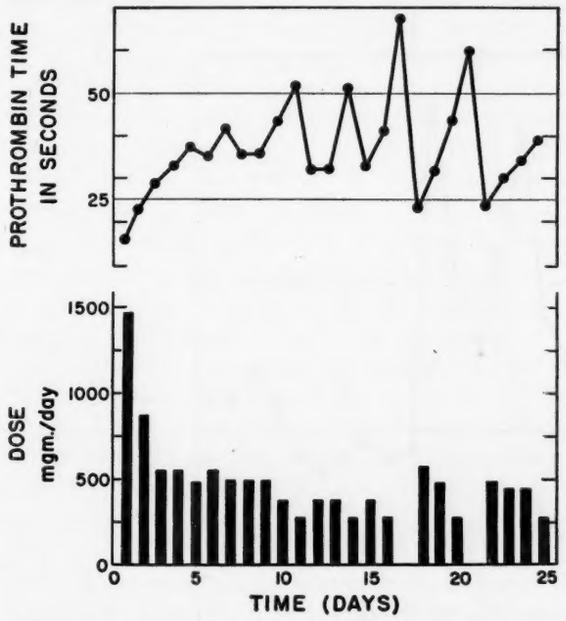

FIG. 2. Patient B. Days 1 to 2: prothrombin response in therapeutic range not achieved until forty-eight hours in spite of large initial dosage and ultimate sensitivity to relatively small maintenance doses. Days 2 to 10: adequate control on an average dose of 500 mg./day. Days 11 to 26: difficulty in maintaining the desired prothrombin response.

achieved for a number of days when suddenly the prothrombin time would abruptly rise to an excessive level. (Figs. 2 to 4.) Omission of a single daily dose in the attempt to offset the sudden hypothrombinemia usually resulted in an abrupt fall to inadequate levels. (Fig. 2.) Attempts were made to correct for a high hypoprothrombinemia by reducing the daily dose but these were not very successful. (Fig. 4.)

Since daily oral doses of tromexan based on the daily prothrombin time frequently resulted in excessive fluctuations in prothrombin activity, other methods of dosage were tried. (1) *Divided oral doses:* Eight subjects who showed wide fluctuations in prothrombin time following the daily administration of single doses of tromexan were given the daily dose of drug divided in three parts at eight-hour intervals; wide and unpredictable prothrombin time fluctuations still occurred in all of the subjects. (2) *Intravenous dosage:* The possibility that the erratic response to tromexan was caused by variations in the rate and completeness of absorption was excluded in three of the aforementioned eight subjects who were maintained on daily intravenous doses of tromexan;* unpredictable prothrombin time irregularities still occurred in these subjects.

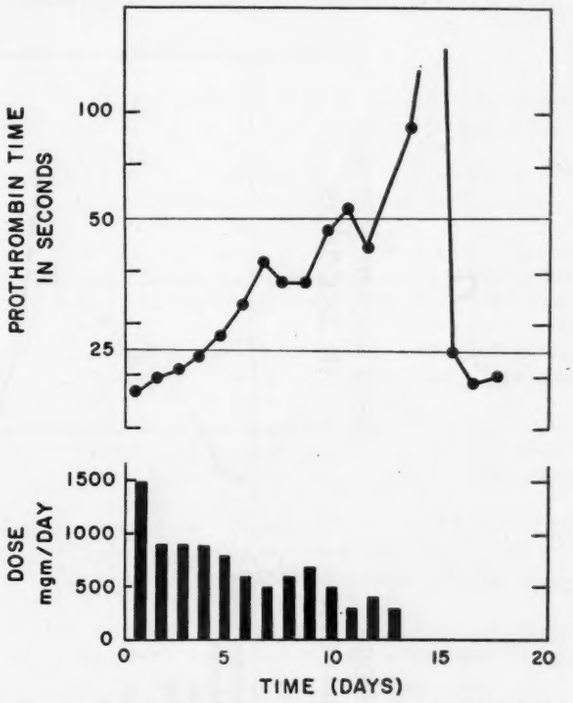

FIG. 3. Patient C. Days 1 to 5: adequate prothrombin response not achieved until the fifth day following a total dose of 4,200 mg. tromexan administered over a period of four days. Days 4 to 11: gradually rising prothrombin times within therapeutic range. Days 12 to 14: excessive rise in prothrombin time in spite of reduced dose; mild bleeding about lips and tongue noted in evening of fourteenth day. Day 15: Prothrombin time greater than 5 minutes ("no clot"). Generalized oral mucous membrane bleeding; vitamin K given intravenously. Day 16: bleeding ceased; precipitous drop in prothrombin time. Days 17 to 18: prothrombin time normal.

Toxic Effects. Three hemorrhagic episodes were noted, none serious in nature: (1) An adequate prothrombin response in a sixty year old woman with arteriosclerosis and bronchial asthma was not achieved until the fifth day of therapy; the prothrombin time then arose progressively in spite of decreasing daily doses. (Fig. 3.) The prothrombin time rose abruptly on days twelve and thirteen and was over five

* Tromexan for intravenous administration was prepared as follows: 50 gm. of tromexan and 12.5 gm. of sodium hydroxide were dissolved in a liter of water and the resulting solution was sterilized by filtration through an Ertell filter. The tromexan in this solution is stable for a period of at least three weeks.

minutes on day fourteen. At this time oral and nasal bleeding developed. Administration of the drug was terminated and water-soluble vitamin K was given intravenously. Bleeding stopped within twenty-four hours and the prothrombin time returned to the pretreatment level within two days. (2) An eighty year old bedridden male with a long history of arteriosclerotic heart disease and auricular fibrillation had had a recent embolus to the foot. On the twelfth day of tromexan therapy extensive ecchymoses developed with a prothrombin time of forty-two seconds. Four days after dosage was terminated the prothrombin time was still at twenty-five seconds. (3) A sixty-two year old patient with coronary heart disease was observed to have gross hematuria on the third day of tromexan therapy; the prothrombin time was thirty-one seconds.

An additional subject abruptly developed an excessive response (112 seconds) on the sixth day of therapy. The drug was discontinued and on the following day the prothrombin time was forty seconds. The patient died of a cerebrovascular accident on the eighth day. No post-mortem examination was made. The role of tromexan in the causation of death in this patient cannot be assessed.

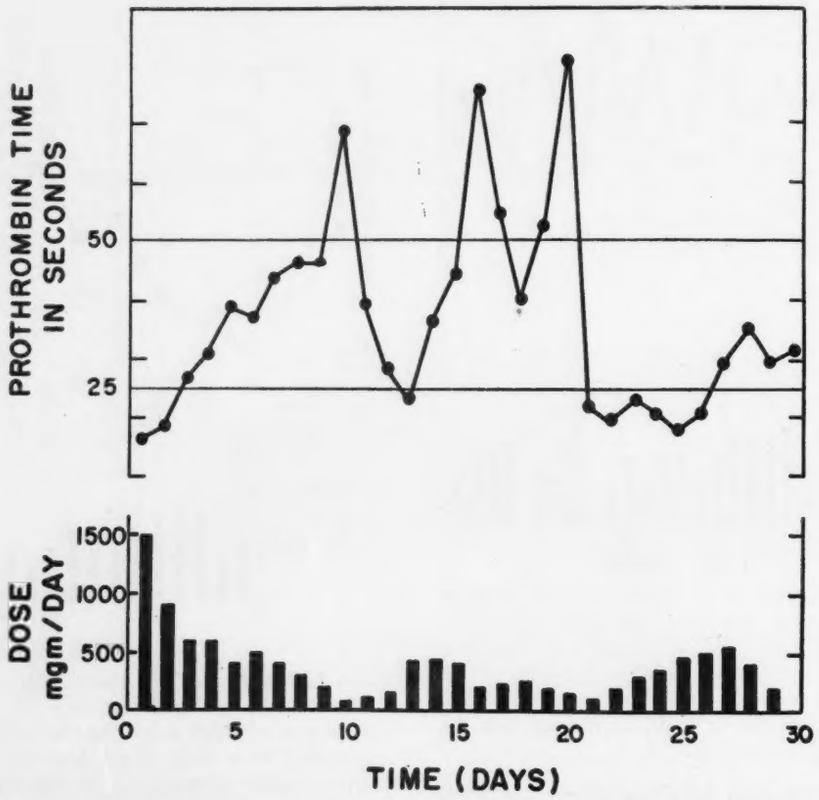

FIG. 4. Patient D. Days 1 to 2: prothrombin response in therapeutic range achieved in forty-eight hours following two large initial doses. Days 3 to 10: progressively increasing prothrombin time in spite of decreasing daily dosage. Days 11 to 13: small doses are followed by rapid fall in prothrombin time. Days 14 to 19: doses divided into three equal parts daily; excessive erratic responses to relatively small total doses. Day 20: precipitous drop in prothrombin time following a single injection of 150 mg. water-soluble vitamin K. Days 21 to 27: inadequate prothrombin response although dosage is greater than that which caused an excessive response the previous week.

COMMENTS

The prompt prothrombin response noted after oral administration of tromexan is in part due to its rapid absorption. It would be expected that the prothrombin response of subjects would reach the therapeutic range in a relatively short period of time. In practice, however, the potential advantage of its rapid absorption is not of material value since there

are wide individual variations in the dose necessary to produce a rapid response of the desired magnitude. A dose of 20 mg. per kg. will raise the prothrombin response of some subjects to the therapeutic level within twenty-four hours, but in others two or more days of further dosage are required in order to achieve the desired level. A larger priming dose is hazardous since with the dose of 20 mg. per kg. a certain number of individuals reach prothrombin times beyond the desired therapeutic range. The rapid metabolic transformation of tromexan is of advantage in those cases in which excessive hypoprothrombinemia with or without bleeding is encouraged. When administration of the drug is discontinued, the prothrombin time usually quickly returns to the pretreatment level.

The chief disadvantage of tromexan lies in the unpredictable fluctuations in response to the drug. Even under the best of circumstance tromexan does not yield as smooth a prothrombin response as does dicumarol.

CONCLUSIONS

1. Wide individual differences in response to tromexan make it difficult to determine that initial dose which will result in an adequate prothrombin response within twenty-four hours. Of fifty subjects given 20 mg./kg. there were two with excessive responses, fifteen with the desired response within twenty-four hours and thirty-three who required additional doses before achieving the desired response.

2. Maintenance doses may vary from 150 mg. to over 1,000 mg. per day.

3. Sudden unpredictable changes in prothrombin time with patients receiving regular daily doses of tromexan are frequent. Correction of these changes by readjusting dosage is frequently difficult.

4. The safe administration of tromexan requires at least daily prothrombin time estimations. In most instances discontinuing dosage results in a rapid return of prothrombin time toward normal.

5. It seems more difficult to achieve clinical control of reduced prothrombin activity with tromexan than with dicumarol.

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Clinical Evaluation of Ethyl Biscoumacetate (Tromexan)*

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ETHYL biscoumacetate, or 3,3-carboxymethylene bis-(4-hydroxycoumarin) ethyl ester, (tromexan®),† a synthesized coumarin ester related to dicumarol,® was first used clinically by Reinis and Kubik[1] in 1948. Several investigators have noted its rapid onset of action and return to normal, as well as its lesser potency milligram for milligram, when compared with dicumarol.[1–6] Some have suggested that tromexan's greater solubility and more rapid absorption and excretion are probable reasons for these characteristics.[6] Most workers[1,5,7,8] have found this drug to be about 20 to 30 per cent as potent as dicumarol.

Some investigators have compared tromexan serum levels with its prothrombin effects.[9,10] It has been suggested that divided daily dosage offers better control and that prothrombin determinations can be spaced at several-day intervals with safety. Other workers believe that if comparable degrees of hypoprothrombinemia are maintained, therapy with tromexan is attended with approximately the same risk of bleeding as dicumarol.[7,11] Because such observations influence the use of this drug in anticoagulant therapy, it was thought worth while to report our clinical experience in a general hospital with patients treated both therapeutically and prophylactically.

A clinical evaluation of tromexan was carried out while treating 116 patients at the Pennsylvania Hospital. The drug was used therapeutically in seventy patients and prophylactically in forty-six. Ages of the patients ranged from seventeen to seventy-eight years. All forty of the males treated were therapeutic cases. Of the seventy-six females thirty were treated therapeutically. Diagnoses of the seventy therapeutic cases were: myocardial infarction, thirty-nine; thrombophlebitis, twenty-five; pulmonary embolism, four (two accompanying obvious thrombophlebitis); arterial occlusion, two and cellulitis of the face and femoral artery embolism, one each. The forty-six patients treated prophylactically, all females, were postoperative patients from the Division of Obstetrics and Gynecology. In these patients the first dose was given nine to twelve hours after surgery and therapy was continued for five to ten days. At this time most patients were fully ambulatory. Upon discharge a therapeutic level of hypoprothrombinemia was present in some patients and decreasing daily doses were given at home without further testing. Through the cooperation of the Divisions of Medicine, Surgery, and Obstetrics and Gynecology an anticoagulant team was permitted to observe and treat patients with thromboembolic disease on these services. With few exceptions all anticoagulant therapy was prescribed by a member of this team.

The *initial dose* was influenced by several factors: Patients with hepatic or renal disease, acute infection, fever or malnutrition usually require smaller dosage.[12] Induction employing heparin or similarly acting drugs has a definite though transient effect on prothrombin time values, so whenever possible control specimens were collected before any anticoagulant was given. Such effects, however, should not persist appreciably longer than the change in the Lee-White venous clotting time. Prothrombin time determinations were made according to the one stage Link-Shapiro modification of the Quick technic using undiluted plasma and a standard thromboplastin material. The control was from

† Supplied by Geigy Pharmaceuticals, Division of Geigy Co., Inc., New York, N. Y.

* From the Cardiovascular Department of the Pennsylvania Hospital. This study was aided in part by a grant from the American Heart Association.

twelve to sixteen seconds and tests were reported in both seconds and per cent. Eliminating those who lacked control prothrombin time data or had been induced with dicumarol and those whose induction was interrupted, there was a total of eighty-nine patients. In this group the average control prothrombin time, expressed as per cent of normal, was 67 per cent for the fifty-one therapeutic cases and 77 per cent for the thirty-eight patients treated prophylactically. Blood specimens for prothrombin time determinations were collected at approximately 10 A.M. and tromexan was ordered and given at about 4 P.M. daily. The effect of the first day's dose was thus usually measured approximately eighteen hours later. This interval between doses was often necessarily less in patients admitted in the late afternoon and in those first treated nine to twelve hours after operation. In such instances, of course, the next day's prothrombin value did not reflect the full effect of the initial dose.

The initial dose of tromexan ranged from 900 to 1800 mg. and seventy-seven of the patients (87 per cent) received 1,200 or 1,500 mg. the first day. Only five were given 900 mg. and in these there were specific reasons for lower dosage. Hepatomegaly with a 30 per cent prothrombin time was the basis in one patient. Two others had low control values of 40 and 42 per cent. A fourth was questionably jaundiced and had a 52 per cent prothrombin time control. The fifth patient had had a drug reaction with leukocytosis, a few red cells in the urine and a prothrombin time of 68 per cent of normal. Second and third doses were based on changes in prothrombin time values. The average second dose was 756 mg. and the average third dose was 516 mg. As can be seen by comparison with the average maintenance dose of 610 mg., the second day's dose was usually slightly greater than the usual maintenance dosage and the third day's dose was nearly the same. Occasionally the second dose was the same as the first. A prothrombin level of 10 to 25 per cent of normal was selected as an adequate therapeutic zone and 15 to 30 per cent of normal as a desirable range for prophylaxis. In tabulating the eighty-nine patients with control prothrombin data it was found that 27 per cent of the therapeutic patients reached the 10 to 25 per cent level the first day of therapy, 80 per cent on the second and 96 per cent by the third day. (Table I.) Of the prophylactic cases 29 per cent reached the 15 to 30 per cent level on the first day of therapy, 82 per cent on the second day and 97 per cent by the third day. Six therapeutic and two prophylactic patients had prothrombin values between 6 and 9 per cent of normal during the first three days of therapy. They are included in Table I. No bleeding occurred in any of these eight patients. Three patients were slow to attain desired levels. Two therapy patients reached 28 per cent of normal on the fifth and seventh days, respectively. One prophylactic patient reached 30 per cent on the fifth day of therapy. The control prothrombin times in these three patients were 80, 72 and 100 per cent of normal. They had all received an initial dose of 1,200 mg. and, in retrospect, should have been given at least 1,500 mg. It is interesting that the second case required an average maintenance dose of 1,100 mg., which is more than usual.

TABLE I
PERCENTAGES OF EIGHTY-NINE (THERAPEUTIC AND PROPHYLACTIC) PATIENTS REACHING SPECIFIC LEVELS OF HYPOPROTHROMBINEMIA WITH TROMEXAN

Days after Therapy Was Started	Zones of Hypoprothrombinemia	
	Therapeutic (51)—10–25% of Normal (%)	Prophylactic (38)—15–30% of Normal (%)
1	27	29
2	80	82
3	96	97
5	98	100
7	100	

Maintenance dosage depends upon the individual patient and his reaction to the drug. As has been noted with dicumarol, there is no uniform rule for dosage. It must instead be based upon repeated determinations of the value of prothrombin in the blood.[7] The average maintenance tromexan dosage and prothrombin time values reported here comprise all values from the third day of therapy, or fourth day of dosage, to and including the last dose and the prothrombin time of the following day. Several principles of therapy have become evident in using this drug. As noted by Burke and Wright,[4,5] in almost every instance daily administration is essential. Omission of one day's dosage usually

results in a rapid return of prothrombin values toward normal and often beyond therapeutic levels. Determination of prothrombin values by the same technician at the same time daily permits better control. The shorter the time between collection of the prothrombin specimen and administration of tromexan the more useful will be the prothrombin report of the next day.

We have used a special anticoagulant sheet with a space for each day on which are listed the control time in seconds, the patient's prothrombin time in seconds, the per cent of normal value and the day's dosage of anticoagulant. Bidaily doses of tromexan were given to a number of patients as some have described.[3,4,8,10,13,14] Usually, in our experience, this procedure did not offer a distinct advantage over the single dose method by which the effect of one dose is measured by the next day's prothrombin value.[4,5] However, two equal doses, one in the early afternoon and the other late in the evening, may offer better controlled hypoprothrombinemia in the occasional patient not adequately managed by single dosage, as has been recently suggested.[15]

Considering fifty-seven patients who received therapy ten days or more there were forty-six, or 81 per cent, who required an average daily maintenance dose between 300 and 900 mg. Average maintenance dosage of this group was 677 mg. The highest average maintenance dose was 1,583 mg. and the lowest was 238 mg. Average prothrombin times of these two patients were 24.4 and 27.5 per cent of normal and they were treated twenty-three and fifteen days, respectively. The greatest total dose was 37,850 mg. in a sixty-seven year old man with myocardial infarction. He was treated for thirty-two days and maintained an average prothrombin time of 25.9 per cent while taking an average maintenance dose of 1,305 mg. a day. This group of fifty-seven patients was chiefly therapeutic; 73 per cent had average prothrombin times between 10 and 25 per cent of normal while 88 per cent had values between 15 and 30 per cent of normal. There was a total of eighty-eight patients in the therapeutic and prophylactic groups who received at least seven days' therapy. This was considered the least time in which maintenance data could be considered reliable. Among the therapeutic patients 74 per cent had average prothrombin times of 10 to 25 per cent, and of those treated prophylactically 59 per cent had average values of 15 to 30 per cent. The lowest average maintenance dose was 238 mg. in a seventeen year old girl with thrombophlebitis who was treated for fifteen days with an average prothrombin time of 27.5 per cent. The largest single dose given to maintain, not to regain, a desired zone of hypoprothrombinemia was 2,100 mg. Although not common, such requirements demonstrate the range of dosage that may be necessary.

The *speed of return to normal of the prothrombin time* after the drug is discontinued is much faster with tromexan than dicumarol. A protective degradation of the drug to tromexan acid A and B, which are relatively inactive and non-toxic, is the probable explanation for tromexan's lack of cumulative action. Von Kaulla and Pulver were unable to recover tromexan from the serum of humans twenty-four hours after a single dose while dicumarol traces remained as long as seven days.[8,9] As has been noted, there is roughly a twenty-four-hour lag between the peak serum level of a single dose of tromexan and that dose's maximal hypoprothrombinemic effect. This reflects the drug's mechanism of action which is through depression of prothrombin formation in the liver.

Data concerning return to a normal prothrombin level were adequate for study in seventy cases. There were several reasons for rejection of the other forty-six patients. Insufficient data were available in thirty-three, usually because the patient was discharged shortly after therapy ended, particularly among those treated prophylactically. Changing the patients to dicumarol for long-term maintenance therapy and death each accounted for five patients. The day after therapy was stopped, or about eighteen hours after dosage was omitted, forty-nine of the seventy patients, or 70 per cent, had prothrombin times of at least 40 per cent. Two days after therapy sixty-seven, or 96 per cent, of patients had prothrombin times of at least 40 per cent. On the third day after omitting therapy two more cases were above 40 per cent and on the fourth day the last patient reached this level. These values are shown in Table II.

In order to eliminate any error that might occur because of poor levels of therapeutic hypoprothrombinemia toward the end of therapy, forty-seven patients with prothrombin times between 10 and 25 per cent of normal the last day of therapy were followed toward normal. Among them 64 per cent were 40 per cent of normal or

higher the day after therapy was stopped and 96 per cent were so by the following day. (Table III.)

There were no instances of *excessive hypoprothrombinemia* as the result of therapy which were not easily and quickly controlled. This was

TABLE II
THE RETURN TOWARD A NORMAL PROTHROMBIN TIME OF SEVENTY PATIENTS AFTER CESSATION OF THERAPY WITH TROMEXAN

Days after Therapy Was Stopped	Hours after Last Dose Was Omitted	Per cent of Patients Reaching 40% or More of Normal
1	18	70
2	42	96
3	66	99
4	90	100

usually accomplished by omitting the drug for one or two days and only rarely were transfusions or vitamin K or K_1 preparations[16] needed. Figure 1 shows the rapid return toward a normal prothrombin level in three patients (not in this series) who had marked hypoprothrombinemia following tromexan dosage. Because of the danger of postoperative bleeding blood and vitamin K_1 oxide®* were given to two of the three patients. No bleeding occurred.

Bleeding did occur in several patients but in

TABLE III
THE RETURN TOWARD NORMAL OF FORTY-SEVEN PATIENTS WITH PROTHROMBIN TIMES OF 10 TO 25% OF NORMAL ON THE LAST DAY OF THERAPY

Days after Therapy Was Stopped	Hours after the Last Dose	Per cent of Patients Reaching 40% or More of Normal
1	18	64
2	42	96
3	66	98
4	90	100

none was it a serious problem. Slight transient bleeding occurred in six patients following hysterectomy. In one the prothrombin level was below 10 per cent of normal the day before a wound hematoma appeared. Omission of that day's dose restored control yet a hematoma occurred four days later when the prothrombin time was 46 per cent of normal. Four other patients had slight vaginal bleeding when the prothrombin times were 21, 48, 52 and 52 per cent of normal, respectively. Cessation of therapy and 1.0 gm. of vitamin K_1 oxide intravenously proved sufficient in one. Ligation of a bleeding point was effective in the second patient and tromexan was not continued. In the third patient the drug was stopped temporarily and therapy was resumed three days later. In the last patient only one dose of 900 mg. was given. Therapy was discontinued because of bleeding at the operative site on the day after surgery though the prothrombin time was 52 per cent of normal. No other therapy was given but death occurred on the sixth postoperative day from pulmonary embolism (see case reports). The sixth patient bled nine days postoperatively, prothrombin times the preceding two days being 24 and 28 per cent. A bleeding vessel in the vagina was sutured. In such postoperative patients, of course, occasional bleeding occurs without anticoagulant therapy. Tromexan, therefore, was not believed a constant causative factor. Slight epistaxis in a patient whose prothrombin time was 22 per cent of normal stopped spontaneously while therapy was continued. A patient with thrombophlebitis experienced hematuria and abdominal pain. One dose of tromexan was omitted and 500 cc. of blood were given, prothrombin values having fallen to 8 per cent of normal. A renal calculus was diagnosed clinically but not proven. Both pain and hematuria stopped promptly and therapy was resumed the following day. Another patient with thrombophlebitis, diabetes, pneumonitis and acute cystitis experienced gross hematuria before tromexan therapy as well as following catheterization during therapy. Recovery was spontaneous each time and dosage was continued.

There was no evidence of sensitization, allergy or untoward reaction to the drug in this series of patients or in a larger group seen since this study. A few patients experienced nausea after the initial dose of usually four or five tablets. This may have been coincidental in the postoperative patients. Such difficulty may be obviated by first giving one-half the initial dose and the other half two hours later.

We have used tromexan freely with dicumarol, heparin® and paritol® (sodium polyanhydromannuronic acid sulfate.)* In its use

* Supplied by Merck & Co.

* Supplied for clinical investigation by Wyeth, Inc.

with dicumarol induction of therapy was usually effected with tromexan alone. After a variable time a gradual transition to dicumarol was accomplished in three or four days by concomitant use of the drugs. This offered no difficulty. It was found that the effects of the two drugs are additive. In using tromexan with parenteral anticoagulant drugs it is essential to have a control prothrombin time before any therapy is begun. It must also be remembered that heparin and related drugs exert a definite lowering effect on the prothrombin level. This is transient but may be very marked one to two hours after intravenous heparin or paritol. For this reason the prothrombin time specimen should be taken just before the next dose of heparin is due. We usually begin therapy of acute venous thrombosis with heparin or paritol given intravenously. If tromexan is started just after such initial dosage, treatment with tromexan alone is possible after twenty-four to thirty-six hours without loss of anticoagulant effect.

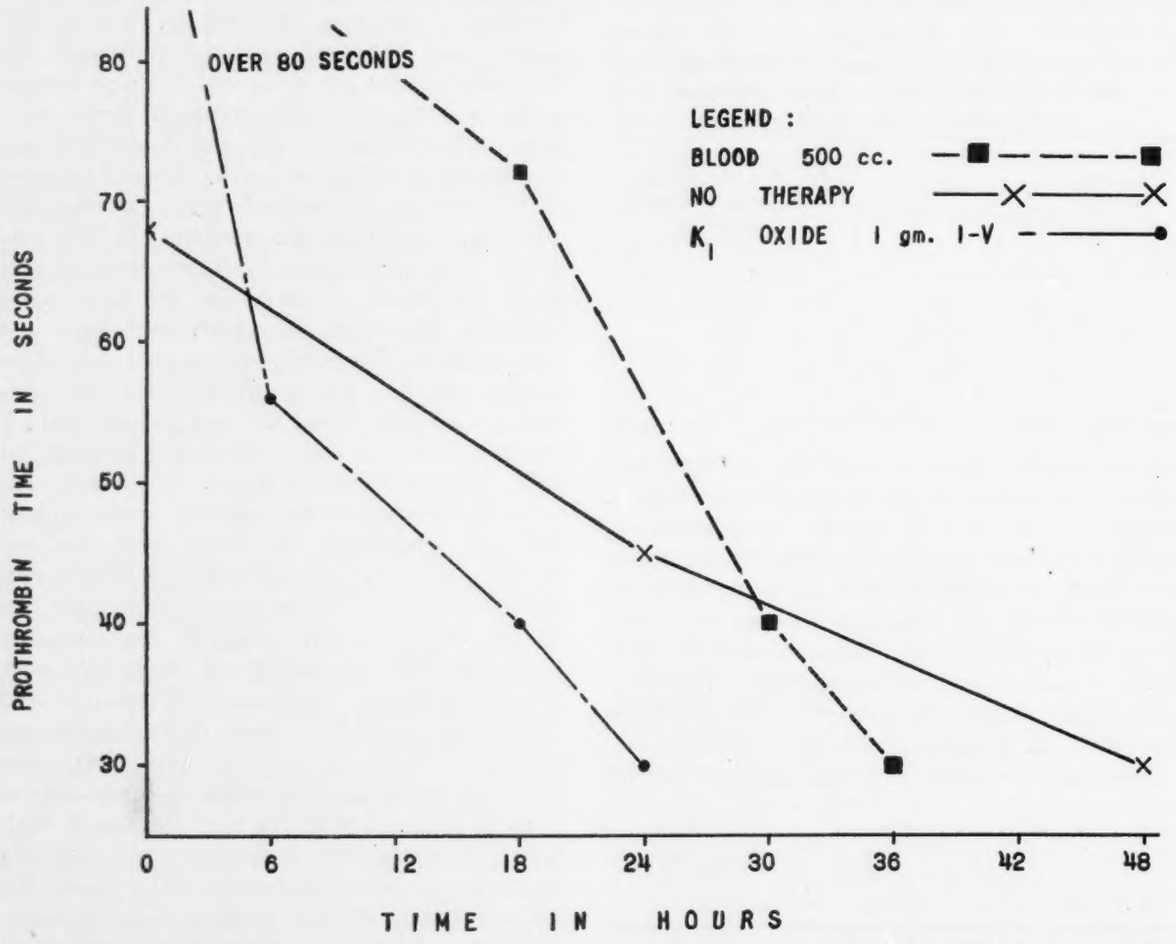

FIG. 1. Return toward a normal prothrombin time in three patients with severe hypoprothrombinemia induced by tromexan therapy. The drug was discontinued and no therapy was given one patient. The two others received 500 cc. of blood and 1.0 gm. of vitamin K_1 oxide (intravenously), respectively. The control time was fourteen seconds. Note the rapid return to a "safe" level within twenty-four and thirty-six hours in the two treated patients despite very high prothrombin times.

By an improved spectrophotometric method recently described by Rieders and Gruber,[17] and through their cooperation, plasma tromexan levels were determined in four patients with diseases not associated with thromboembolism. Maximal plasma concentration occurred between four and one-half and eight and one-half hours, averaging six and one-half hours, and ranged from 2.75 to 11.6 mg. per 100 cc. of plasma following a single dose. The patient requiring eight and one-half hours received 1,200 mg. of tromexan; the other three patients received 2,100 mg. Other investigators using an

earlier photometric method reported that maximal values were reached between three and six hours.[9,10] With the spectrophotometric method we learned that tromexan was present in the plasma after four hours in amounts ranging from 0.2 to 4.6 mg. per 100 cc. of plasma. After twenty-four hours only insignificant amounts, from 0.1 to 0.3 mg., remained.

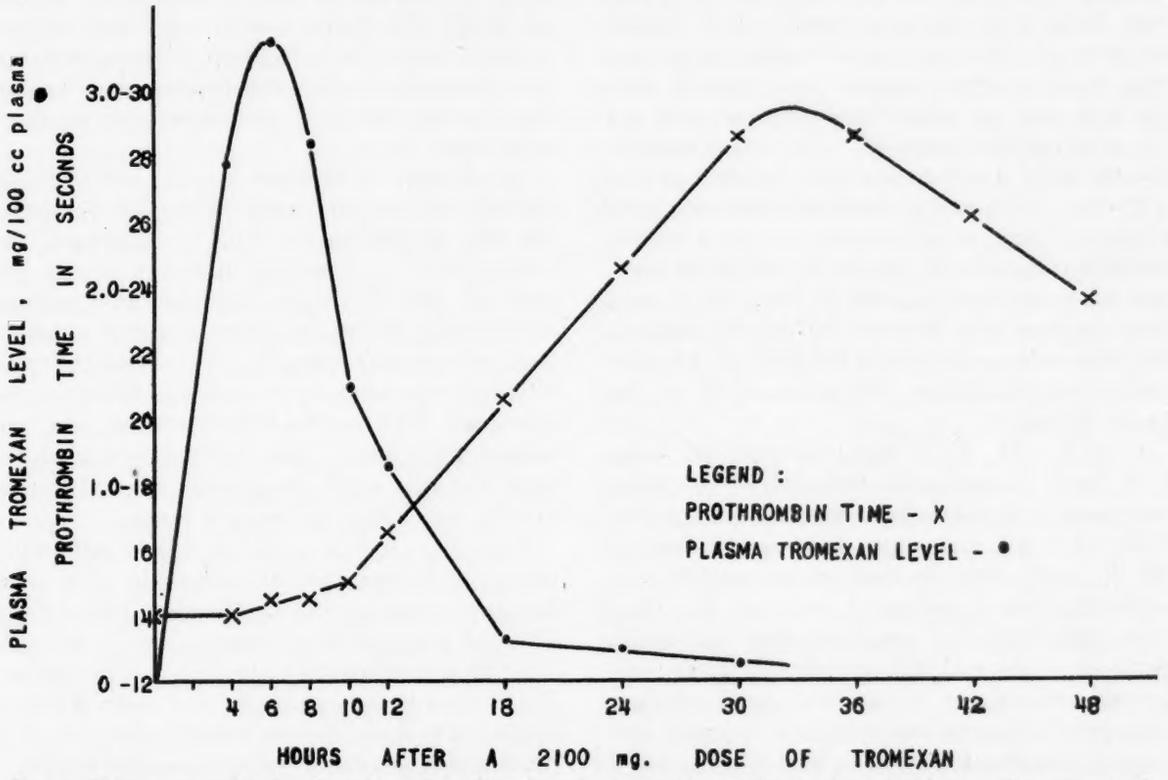

FIG. 2. Plasma tromexan levels and prothrombin times in two patients who received 2,100 mg. of tromexan one and one-half hours after breakfast. The curves are the average values of the two patients.

In order to compare plasma tromexan levels and prothrombin time changes these determinations were made simultaneously in two patients. Both of these persons were well nourished, afebrile and eating regularly. Each was given a single 2,100 mg. dose of tromexan one and one-half hours after breakfast. Specimens were collected, oxalated, centrifuged and the plasma was frozen to permit study later. The values obtained are plotted in Figure 2. First changes in the prothrombin time occurred from six to twelve hours after dosage in these patients from whom specimens were taken at four, six, eight, ten and twelve hours and then every six hours. Control prothrombin times were 80 per cent of normal in both instances (standard control—twelve seconds; patient's time—fourteen seconds). Peak levels of hypoprothrombinemia, twenty-nine seconds (22 per cent) and thirty-seven seconds (15 per cent), were attained twenty-seven and thirty-seven hours after dosage. Levels of 25 per cent of normal were reached within twenty-five hours in both of these patients. This is similar to the experience with animals as well as in man, as reported by other investigators.[1,6,10,12,13]

There were five deaths (4 per cent) in this series of patients. The first, a thirty-six year old female, was being treated prophylactically but tromexan therapy was stopped because of bleeding at the site of a laparotomy wound. Several days later she died of pulmonary embolism. The other four patients were in the therapeutic group. Pulmonary infarction from adherent mural thrombi of the heart, probably secondary to myocarditis, occurred despite adequate hypoprothrombinemia in a thirty-six year old man. A third death occurred from recurrent myocardial infarction in a diabetic whose level of hypoprothrombinemia was not well maintained. The fourth patient died from progressive myocardial damage. The last patient also died of severe cardiac disease. More detailed reports of these patients follow.

CASE I. M. A., a female thirty-six years old, had had an abdominal hysterectomy, salpingo-oophorectomy and appendectomy for myoma uteri October 27, 1950. Preoperatively the control prothrombin time was 60 per cent of normal. Six hours after operation 900 mg. of tromexan were given. The next morning, sixteen hours later, the prothrombin time was 52 per cent and bleeding was noted at the operative site. Anticoagulant therapy was stopped after the first dose and the second postoperative day the prothrombin time was 16 per cent of normal. On the third day the value was 56 per cent and a fever of 101°F. and abdominal tenderness were present. These were thought due to a subcutaneous collection of blood. On the sixth postoperative day she experienced severe chest pain and dyspnea and died within fifteen minutes. Permission for autopsy was not granted. Massive pulmonary embolism was believed to be the cause of death.

CASE II. M. S., a thirty-six year old male, had been hospitalized frequently for acute pulmonary edema. He was discharged July 19, 1950, after his sixth entry but was readmitted on the same day because of hemoptysis and vomiting. He experienced pain in the right chest July 28th and again coughed up blood. Both an x-ray and an electrocardiogram suggested pulmonary embolism. Anticoagulant therapy was begun using heparin initially and starting tromexan the fourth day. On the third and fourth days of heparin therapy chest pain recurred and was believed due to further pulmonary emboli.

A therapeutic prothrombin level, 10 to 25 per cent of normal, was reached the day after tromexan was first given (the fifth day of therapy) and was maintained until the patient died August 6, 1951. Autopsy revealed changes consistent with Fiedler's myocarditis and mural thrombi. Death resulted from pulmonary infarction and cardiac failure. Anticoagulant therapy was not considered a contributing cause of death. No abnormal bleeding was noted either clinically or at autopsy.

CASE III. L. T., a fifty-nine year old male, received dicumarol in November and December, 1948, for an acute anterior myocardial infarction. Diabetes mellitus was found and controlled by diet alone. He was readmitted on January 11, 1951, with a second acute myocardial infarction. Anticoagulant therapy was started with tromexan and insulin was given to control the diabetes. Digitalis and procaine penicillin were used to combat cardiac failure and pneumonitis. On January 23rd he became unable to speak. A positive Hoffmann sign and hyperactive motor reflexes were present on the right side and facial weakness on the left. The heart was regular and there were basal pulmonary rales. His course was downhill and he died January 26th. Anticoagulant therapy was not well maintained, the prothrombin level having risen to 40 per cent of normal or more on three occasions.

At autopsy a massive infarct involved the lateral and anterior walls of the left ventricle. An old healed apical infarct explained the earlier episode. A mural thrombus of the left ventricle accounted for multiple renal infarcts which were found. A right occipital cerebral hemorrhage was thought to be embolic also although spontaneous hemorrhage could not be excluded. The cerebral hemorrhage was too remote from motor areas to explain neurologic signs which were considered secondary to anoxia rather than an organic lesion.

CASE IV. J. W., a fifty-five year old male, first experienced cardiac failure in 1937 and had been cared for in the Cardiac Clinic since 1949 with digitalis, mercurials and a low salt diet. He was admitted to the hospital December 25, 1950, with intractable heart failure. Electrocardiogram showed sinus tachycardia, frequent premature ventricular contractions and evidence of a myocardial infarct of indeterminate age. Anticoagulant therapy was begun with tromexan. Progressive failure continued despite all therapy. He died on the thirteenth hospital day.

Autopsy showed diffuse myocardial fibrosis and hypertrophy, a posterior wall infarction of probably several months' duration, and mural thrombi. Multiple renal infarcts were found bilaterally. A prothrombin level of 22 per cent of normal was present the day before death. No hemorrhages were found at autopsy.

CASE V. M. P., a sixty-five year old female, had attended the clinic fourteen years for hypertensive and arteriosclerotic heart disease with angina pectoris. She was hospitalized December 28, 1950, with acute pulmonary edema after having stopped digitalis. Oxygen, morphine, digitalis, mercurials and rotating tourniquets were employed. An electrocardiogram showed a left bundle branch block with premature auricular and ventricular contractions. Anticoagulants were started as recent

infarction was suspected. Using tromexan a therapeutic level was reached the third day of treatment and prothrombin time values ranged between 12 and 28 per cent of normal, averaging 20.5 per cent. On January 9, 1951, while on a bedpan, the patient suddenly collapsed and emergency measures were of no avail. The prothrombin time had been 12 per cent of normal the preceding day when she was given 900 mg., her average maintenance dose.

Autopsy findings were myocardial hypertrophy, severe coronary arteriosclerosis and extensive myocardial infarctions, one recent and another old. Recent microscopic hemorrhages were found in the healed infarct, lung and spleen. Hypertension and a therapeutic hypoprothrombinemia were believed causative factors in the microscopic hemorrhages. There was no evidence of pulmonary emboli.

COMMENTS

The effectiveness and safety of anticoagulant therapy with tromexan, as with dicumarol, depends on adequate and reliable laboratory data. During the period of induction and for many days thereafter daily prothrombin time determinations are desirable. In most patients daily tests were done except on Sundays when the test was often omitted without difficulty. No fewer tests were done than would have been considered necessary with dicumarol. Control tests were taken routinely before therapy was started even though the first dose of the drug at times was given before a report was obtained. When necessary the control plasma specimens were frozen for later determination. No obvious hematologic, renal or hepatic toxic effects were seen in any of the patients of this study or in a larger subsequent group of patients.

In determination of the dosage necessary for induction as well as maintenance, several factors in addition to daily prothrombin determinations are of concern. Body weight seems to be relatively insignificant but the general condition of the patient is important. If he is poorly nourished or if there is functional impairment of the liver or kidneys due to disease or congestion from cardiac failure, smaller than average dosage should be considered for induction and maintenance. Cardiac patients with congestive heart failure and hepatomegaly are often difficult to control with either tromexan or dicumarol. Severely ill patients whose fluid balance and caloric intake may be disturbed usually need smaller dosage. In those patients with control prothrombin times below 50 per cent of normal more cautious induction was undertaken. It is of interest, too, that there was no significant correlation, statistically, between control prothrombin time values and average maintenance dosage in this series. We have observed that daily fluctuations in prothrombin time levels tend to be greater with tromexan than with dicumarol. A single day's prothrombin value must not be considered alone in determining maintenance dosage but rather in relation to the trend of the prothrombin curve. In a curve that is rising toward normal greater dosage will be necessary to achieve desired zones of hypoprothrombinemia than with the same prothrombin value in a falling curve. One can be nearly certain that the prothrombin time (in seconds) will fall the day after the last dose of tromexan is given. This is certainly not true of dicumarol therapy in which the time may often be prolonged for one or more days after therapy. Regularity in the time of specimen collection and dosage administration is also more essential with tromexan. The sooner the drug is given after the prothrombin time has been determined the more consistent the therapy. Divided daily dosage has been suggested to help overcome these disadvantages although this is not generally practical.

In anticoagulant therapy with heparin Hedenius[21] has suggested a gradual withdrawal of the drug at the end of treatment. This principle may be of importance in tromexan therapy because of the rapid return of the prothrombin level to normal upon stopping this drug. For this reason we have recently followed the practice of "tapering off" anticoagulant therapy by giving decreasing doses of tromexan over several days. With dicumarol the more gradual return to normal makes the possibility of complications from "rebound" phenomena seem less likely. In our experience as well as that of Gruber[18] tromexan is nearer one-tenth to one-eighth the potency of dicumarol, on a milligram per milligram basis, rather than one-fifth to one-third the potency as has been reported.[1,5,7,8] Variations in individual sensitivity to dicumarol, as noted by Link[19] and James,[20] occur also with tromexan and probably as frequently. Several patients showed considerable variation in their individual dosage requirements during treatment.

With special or complicated therapy tromexan has both advantages and disadvantages. For

long-term therapy extending over a period of many weeks or months dicumarol seems preferable. Expense may be an important factor for many such patients. A stable level of hypoprothrombinemia is more easily maintained with dicumarol and less frequent prothrombin tests may be needed. For prophylaxis in surgical and obstetrical patients, in whom the chance of bleeding is potentially greater, tromexan is a more satisfactory anticoagulant. Control of dangerous levels of hypoprothrombinemia is usually accomplished within twenty-four hours by stopping the drug. The response to administration of vitamin K_1 preparations or whole blood, if bleeding occurs, is more rapid than with dicumarol. Use of vitamin K preparations, plasma or whole blood just before or during anticoagulant therapy may change a patient's response to anticoagulants and thereby complicate treatment, as has been reported.[22]

SUMMARY

1. A new coumarin drug, Tromexan, was evaluated clinically in 116 patients on therapeutic and prophylactic regimens.

2. Control prothrombin times were taken on all patients. The initial dosage of 900 to 1,800 mg. (usually 1,200 or 1,500 mg.) was determined by this and other factors. Subsequent dosage was judged by daily prothrombin time determinations. Daily maintenance dosage ranged from 300 to 900 mg. and averaged 677 mg. in a group of fifty-seven patients treated for ten days or more. No fewer prothrombin time determinations were needed than would have been considered essential with dicumarol therapy.

3. More than one-fourth of the patients reached desired levels of hypoprothrombinemia in less than twenty-four hours and more than 80 per cent by the end of forty-eight hours. Following cessation of dosage 70 per cent of patients had prothrombin values of 40 per cent the following day. Two days after therapy was stopped 96 per cent had prothrombin values above this level.

4. There was greater variability in the daily prothrombin levels than we have experienced with similar patients receiving dicumarol. For well controlled therapy the drug must be given at nearly the same time each day and relatively soon after the prothrombin test is done. Severe hypoprothrombinemia was less of a clinical problem than with dicumarol therapy, however, because of the rapid cessation of the effect of a single dose and the rapid response to vitamin K_1 preparations. Bleeding occurred in several patients, especially in the prophylactic group, but in none was it a serious problem.

5. No difficulty was encountered in giving the drug with either heparin or dicumarol for induction or maintenance.

6. Gradual withdrawal of the drug at cessation of therapy by "tapering off" of dosage is probably important in the prevention of relapse or recurrence of thrombotic processes.

7. Special studies of plasma concentration after oral dosage were made in four patients. Appreciable amounts of tromexan were present after four hours and insignificant amounts remained after twenty-four hours. In two of these coincident prothrombin time determinations demonstrated a level of 25 per cent of normal after twenty-five hours.

8. From our experience with these and a subsequent larger number of patients it is our opinion that tromexan has no great advantage over dicumarol for routine therapy. The advantages of prompt onset and cessation of effect may be offset by the necessity for precise timing of administration. It is a more useful drug for short term and prophylactic therapy in surgery and obstetrics but less satisfactory for long term treatment, in which infrequent prothrombin time determinations and stable levels of hypoprothrombinemia are desired.

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Clinical Use of a New Anticoagulant, Phenylindanedione*

Report of 400 Cases

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In 1947 Soulier and Gueguen[1] used phenylindanedione as an anticoagulant. This substance had first been described in 1944 by Kabat, Stohlman and Smith.[2] Much of the fundamental work was carried out on this continent by Jaques et al.[3,4] Blaustein et al.[5] reported on the clinical trial of this material in fifty-three cases in May, 1950. This report was followed by a report on 100 treated cases by Blaustein[6] and later on 200 cases.[7] Bjerkelund[8] added to the literature with his observation that vitamin K was antagonistic in action to phenylindanedione. Preston et al.[9] recently reported on the clinical use of phenylindanedione in seventy-four patients.

Initial Dosage. Two hundred to 300 mg. of phenylindanedione† are given initially. We roughly gauged that individuals weighing 150 pounds or less should be given 200 mg. and those weighing over 150 pounds should receive 300 mg. This should be given in two divided doses of 100 and 150 mg. each in the morning and at bedtime.

Frequency of Administration. As in dicumarol therapy, the maintenance dose must be gauged by the prothrombin time performed daily for at least the first four days of therapy. Once the maintenance dose is established less frequent prothrombin time determinations are necessary (once in from seven to fourteen days) depending on individual patient reaction. The average maintenance dose in 400 treated cases was 65 mg./day; the individual maintenance dose varied from 25 mg./day to 100 mg./day. Two patients operated on for intestinal obstruction, who were in a state of inanition at the time, and two in chronic cardiac failure were the four patients who required 25 mg./day of phenylindanedione. Initially we noted daily fluctuations in the prothrombin levels but after following the suggestion of Wright that we split the daily dosage in two the daily prothrombin fluctuations were found to be minimal. Recently, in an article comparing dicumarol,® tromexan,® phenylindanedione and bexycoumarin,® Shapiro[10] stated that the initial dose of phenylindanedione was 900 mg. and that the average daily maintenance requirement was 300 mg./day. These figures were not supported by any case studies and in our experience such doses are far beyond the clinical requirements and would be expected to lead to hemorrhage.

Speed of Action and Recovery. The speed of action and rate of response varied. In twenty individuals the desired prothrombin level was reached in less than twenty hours. In two hundred seventy-four cases it was reached in twenty-eight hours or less. Eighty-two cases showed adequate hypoprothrombinemia in thirty-two hours. Nine cases took fifty-four hours to reach the desired prothrombin level and fifteen cases never reached the degree of hypoprothrombinemia desired, despite the use of large doses.

The rate of recovery was forty-eight hours or less in 386 cases. The remainder showed complete recovery in 72 to 144 hours. Alexander[11] stated that he had noted a delayed reaction to phenylindanedione, suggesting cumulative action. We did not observe this.

Individual Reactions and Toxicity. Jaques et al.[3,4] in their experimental work noted hemorrhage in two dogs that had been given doses of phenylindanedione far greater than would be given to humans. Soulier and Gueguen[1] noted

† For our recent work Hedulin®-phenylindanedione was kindly supplied by Dr. H. E. Dubin, Walker Laboratories, Mt. Vernon, N. Y.

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renal damage in the form of hematuria, blood casts and crystal formation, presumably due to deposition of phenylindanedione in the tubules. However, the doses they used were far beyond the clinical requirements.

We did daily urinalyses in our earlier series of cases and found no urinary changes. In 400 treated cases we had two patients who showed hematuria. One of these had one urine sample in which blood was found. The second case was that of a fourteen year old girl treated for chronic thrombophlebitis of unknown etiology. She tolerated the drug well and responded clinically for ten days. At this time she was discharged and sent home on a maintenance dose of phenylindanedione. Forty-eight hours later she had hematuria, passed large clots of blood and palpation of the kidneys revealed large bilateral masses which were believed to be perirenal hematomas. The prothrombin time was 28 seconds with a control of 16 seconds. Since the amount of bleeding was far out of proportion to the hypoprothrombinemia, the authors did not ascribe the hemorrhage in this case to the anticoagulant. Eight days later intravenous pyelography revealed a suspicious mass in the upper pole of the left kidney and it was decided to do an exploratory laparotomy. At operation bilateral polycystic kidney disease was noted. Many of the loculated cystic spaces were filled with blood.

TABLE 1*

Type of Case Treated	No.	Average Maintenance Dose (mg./day)	Resistant Cases		Hemorrhage		Ill Effects
			Initial	Delayed	Minor	Major	
Acute coronary thrombosis.....	116	65	2	1	2	0	
Chronic myocardial insufficiency....	148	65	8	0	0	0	Diarrhea (one case)
Thrombophlebitis.....	136	65	5		1	0	

* The average time taken for prothrombin level to be reached was less than thirty-two hours; the average time taken for return of prothrombin level to normal was less than forty-eight hours.

Resistance to Phenylindanedione. A phenomenon recognized early with dicumarol was that of resistance of some patients to the drug. This phenomenon we have also observed with phenylindanedione. The resistant cases we have noted fall into two types: initial resistance, in which adequate hypoprothrombinemia is never obtained, and delayed resistance, in which the patient may respond very well to the drug and then suddenly the prothrombin time returns to normal despite increasing doses of the drug. This occasional inadequate response is the single drawback to the anticoagulant.

We wondered whether the resistance was specifically to phenylindanedione or to oral anticoagulants in general. We gave eight of these patients dicumarol, tromexan and bexycoumarin in succession. Our few observations indicate that there is no specific resistance to phenylindanedione but resistance to oral prothrombopenic drugs in general. We recently observed a case of resistance to dicumarol. The patient treated for thrombophlebitis was given 600 mg. over a three-day period and the prothrombin time was never prolonged beyond 19 seconds, with a 15-second control. This patient was then placed on phenylindanedione, 300 mg. initially followed by 200 mg. the next day and 100 mg. on the third day. The drug was ineffective in altering the prothrombin level.

Effect of Vitamin K on Phenylindanedione. Bjerkelund[8] in his excellent study of phenylindanedione demonstrated unequivocally that vitamin K (water-soluble) was efficacious as an antagonist to phenylindanedione when given intravenously. The authors used vitamin K in one patient in whom the prothrombin time rose to 80 seconds on a single 200 mg. dose of phenylindanedione. The prothrombin time quickly returned to normal but the rate of return differed little from that in patients not receiving vitamin K. We have since used K_1 emulsion and found it to be effective in four hours in bringing the prothrombin level back to normal limits. We have been limited in opportunity to study the antagonistic action of vitamin K, K_1 oxide or K_1 emulsion because in 400 cases we have had only three cases of bleeding, two of minor nature and

the one case of polycystic kidney disease with hematuria in which there was only a moderate prolongation of the prothrombin time.

CONCLUSIONS

Phenylindanedione is an effective, non-toxic anticoagulant which exerts its action far more rapidly than dicumarol.

The weight of evidence is against its showing any cumulative properties. It is rapidly excreted. Usually within six hours of the initial dose the patient notices that his urine is orange-colored, the color of phenylindanedione in alkaline solution.

In 400 collected cases 3.75 per cent were resistant to the drug.

There were three cases of hemorrhage, or 0.75 per cent of all cases treated.

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Review

Serum Cholinesterase in Health and Disease*

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THE cholinesterases constitute a family of enzymes, each tissue having its own.[74] The serum cholinesterase is one of these. Until recently relatively little was known of its properties, its pathophysiology or its fluctuations in health and disease. This was due to the fact that the methods used to determine the activity of the enzyme, principally modifications of the titrimetric method of Willstätter et al.[90] or the gasometric (Warburg) technic of Ammon,[1] were cumbersome, difficult and time-consuming. The development by Michel[56] in 1947 of an electrometric method for measuring serum cholinesterase activity has provided a simple tool for its study in man. In brief, the method measures, with a potentiometer, the drop in pH resulting from the liberation of acetic acid when acetylcholine is enzymatically broken down by the cholinesterase in an unknown sample of serum. The drop in pH is then corrected for non-enzymatic hydrolysis by reference to tables prepared by Michel, and the serum cholinesterase activity is expressed in terms of units of decrease of pH per hour (i.e., Δ pH/hr.).

During the past four years we have used Michel's technic to study changes in serum cholinesterase activity in health and in a variety of disease states. This report deals with the results of these studies and, because of the increasing interest in the enzyme by clinicians, it also summarizes work of other investigators in this field.

NATURE, ORIGIN AND FUNCTION OF SERUM CHOLINESTERASE

The esterases are a widely distributed group of enzymes which catalyze the hydrolysis of esters of various organic acids. In general, they vary considerably with respect to their specificity of action, especially toward the acid component of the ester. However, the cholinesterases are rather specific in their nature since they serve to catalyze the hydrolysis of acetylcholine, the neurohormone of the nervous system.

Engelhart and Loewi[24] conclusively demonstrated the enzymatic action of serum cholinesterase and showed that it hydrolyzes acetylcholine. However, it differs from tissue cholinesterases in being rather non-specific in its action, as Vahlquist[85] indicated. Because serum cholinesterase hydrolyzes many esters, as well as acetylcholine, it has been called serum pseudo-cholinesterase or serum esterase. We prefer to call it serum cholinesterase since acetylcholine bromide or chloride is used as a substrate in Michel's method of assay and because the electrometric technic only measures the ability of the enzyme to hydrolyze the acetyl radical. In the studies reported here no attempts were made to characterize the enzyme or to differentiate serum cholinesterase by using a variety of substrates as suggested by Zeller and his associates.[54,96]

Serum cholinesterase has been isolated from the serum of the horse[80] and man[5] and analysis of human serum cholinesterase indicates that it is probably a mucoprotein with a molecular weight of approximately 165,000, associated with Cohn's plasma protein fraction of IV-6, 95 per cent alpha$_2$ globulin, 5 per cent albumin.[14]

Much evidence has been accumulated to support the concept that the serum cholinesterase molecule is synthesized in the liver,[12,33,45,74,89] probably in parallel with the albumin molecule. In the blood it appears to have a life span of approximately twenty-eight days. Further com-

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ments regarding its synthesis and life span will be made subsequently.

As to its physiologic functions, the cholinesterase of the serum appears to have none that have as yet been clearly demonstrated.[85] By injecting cholinesterase-inhibiting drugs into patients the serum cholinesterase has been reduced to less than 5 per cent of its normal level without the appearance of any clinical symptoms and without the development of any measurable physiologic disturbances.[16,33]

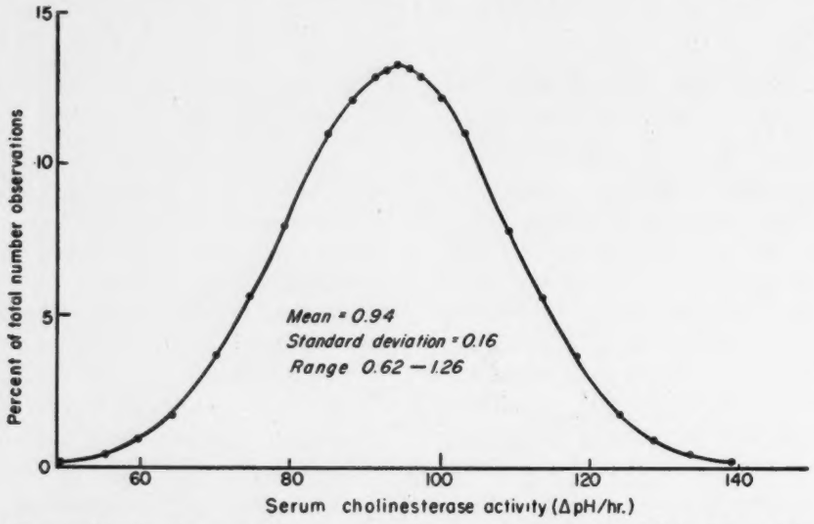

FIG. 1. Distribution curve for serum cholinesterase activity in 120 healthy adult men and women.

SERUM CHOLINESTERASE IN NORMAL INDIVIDUALS

Many investigators have studied cholinesterase activity in healthy people and have emphasized the wide range of variation in enzyme concentration from person to person.[3,13,26,33,48,53,57,85] Using Michel's technic we determined serum cholinesterase activity in 120 healthy individuals. The distribution curve of data from this group is shown in Figure 1. The range of activity was 0.58 ΔpH/hr. to 1.37 ΔpH/hr., with a mean of 0.94 ΔpH/hr. and a standard deviation of 0.16. The normal range, defined as mean plus or minus two standard deviations, was 0.62 ΔpH /hr. to 1.26 ΔpH/hr. Differences in enzyme activity did not correlate with age, sex, weight, height or surface area.

Although there is a wide spread of serum cholinesterase values from one healthy person to the next, the level of cholinesterase is remarkably constant for each healthy, well fed individual, from day to day and from month to month. In fact, we have found neither diurnal nor seasonal fluctuations in serial studies of cholinesterase levels in the blood of healthy persons.

The wide range of normal values described heretofore may occasionally be a source of confusion. We observed a few patients ill with acute viral hepatitis who had serum cholinesterase levels which fell within the lower limits of the normal range. Actually their cholinesterase levels had been depressed by hepatitis because the serum cholinesterase began to climb as they regained their health. When they were quite well, their cholinesterase values reached the upper limits of the normal range. This overlapping of serum cholinesterase values in some of the healthy and in some of the sick is a common biologic phenomenon which sometimes makes interpretation of single measurements difficult.

CONDITIONS IN WHICH SERUM CHOLINESTERASE ACTIVITY IS LOW

Liver Disease and Disease of the Biliary System. When the hepatic parenchyma is diseased, the serum cholinesterase activity is almost invariably depressed. This finding was first observed by Ar[illegible]ool et al.[4] and has since been substantiated by many investigators.[4,13,26,33,45,46,52,86,87] On the whole, the depression in enzyme concentration tends to be somewhat more marked in patients ill with chronic liver disease, such as cirrhosis, than in those ill with acute conditions, such as viral hepatitis, ascending cholangitis and acute anoxic hepatomegaly.

Data from sixty patients ill with chronic diseases of the liver showed a range of serum cholinesterase activity from 0.73 ΔpH/hr. to 0.08 ΔpH/hr., with a mean of 0.41 ΔpH/hr. In thirty-two cases of acute hepatic disorders the range was 0.78 ΔpH/hr. to 0.16 ΔpH/hr., with a mean of 0.49 ΔpH/hr. On the other hand, normal levels of serum cholinesterase activity were found in patients suffering with obstructive jaundice unless this was complicated by considerable hepatic parenchymal involvement. This is an important differential point in diagnosis.[86] Figure 2 illustrates graphically the findings in the three groups of patients.

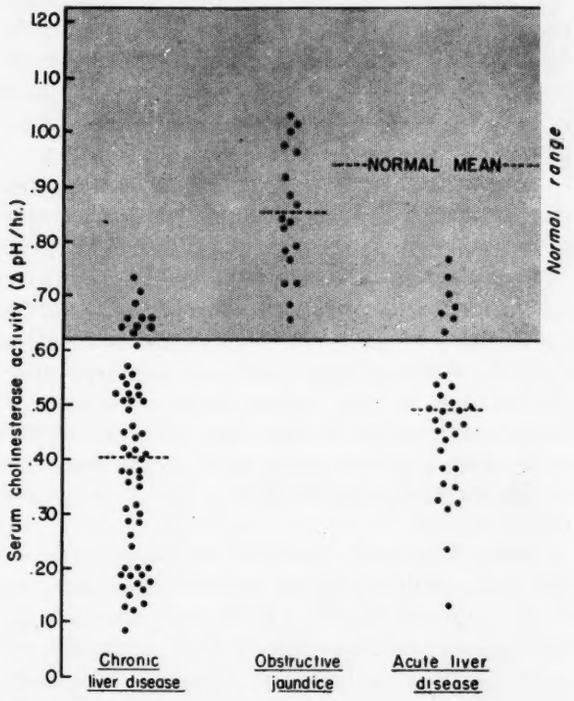

FIG. 2. Scattergram showing serum cholinesterase activity in chronic and acute liver disease and in uncomplicated obstructive jaundice. Each point represents one patient; dotted lines indicate mean values for each group.

Serial studies of serum cholinesterase in both acute and chronic disease of the liver have shown that changes in its concentration closely reflect changes in hepatocellular function. When compared with a battery of ten other commonly employed tests of liver function (serum albumin and globulin concentration; plasma prothrombin time; cephalin flocculation; thymol turbidity and flocculation; serum bilirubin, one minute and thirty minutes; serum alkaline phosphatase; plasma cholesterol, total and esters; bromsulfalein clearance; and two-hour urinary urobilinogen excretion), none appeared to mirror the changing status of the hepatic parenchyma as sensitively as did the serum cholinesterase activity.[86,87] Figure 3 demonstrates changes in serum cholinesterase in a patient ill with homologous serum hepatitis as compared with other liver function tests. As is true of many such patients, this man's convalescence was punctuated by a mild relapse which was not evident clinically. However, the relapse was graphically demonstrated by a dip in the rising concentration of enzyme and the patient was kept in bed until his serum cholinesterase level was steady at its normal value.

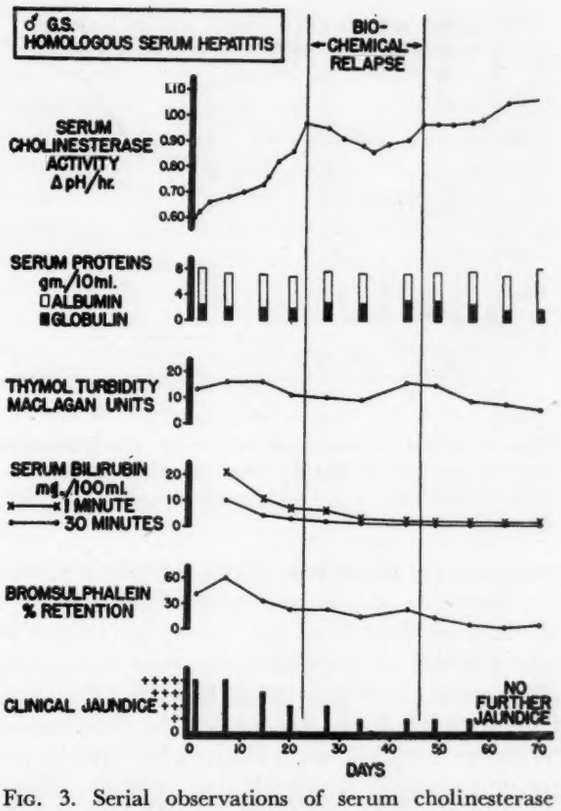

FIG. 3. Serial observations of serum cholinesterase activity and other liver function tests in patient G. S. ill with homologous serum hepatitis. (Vorhaus, L. J., Scudamore, H. H. and Kark, R. M. Measurement of serum cholinesterase activity: a useful test in the management of acute hepatitis. *Am. J. M. Sc.*, 221: 140, 1951.)

We attribute the low serum cholinesterase activity found in liver disease to impaired hepatic synthesis of the enzyme and believe that measurement of serum cholinesterase activity is a useful laboratory tool to aid the clinician in evaluating patients suffering with liver disease. It is particularly valuable in following the course of hepatocellular illness.

In acute hepatitis the cholinesterase level is always subnormal when the disease is ushered in with clinical jaundice. Alterations in the clinical status of the patient are reflected in changes in cholinesterase activity if these are followed serially. Generally four types of change

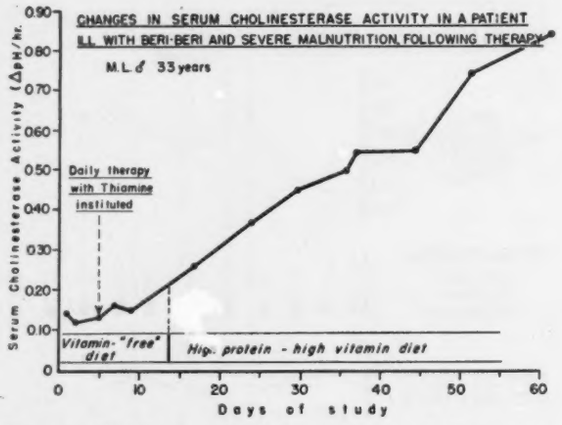
CHANGES IN SERUM CHOLINESTERASE ACTIVITY IN A PATIENT
ILL WITH BERI-BERI AND SEVERE MALNUTRITION FOLLOWING THERAPY
M.L. ♂ 33 years
Daily therapy with Thiamine instituted
Vitamin-"free" diet
High protein - high vitamin diet
Serum Cholinesterase Activity (ΔpH/hr.)
Days of study

FIG. 4. Serial observations of serum cholinesterase activity in a patient ill with "wet" beri-beri and severe malnutrition before and after treatment with thiamine and a nutritious diet.

are seen: (1) Most commonly there is a steady rise from low to normal values which then level off in the normal range. The appearance of this plateau of cholinesterase activity signals the beginning of convalescence. (2) Of course, the recovery of the patient can be punctuated by relapses which are indicated by dips in the rising curve of cholinesterase activity. These depressions may also be seen during the early part of the plateau and then indicate a late relapse. (3) The third type of curve is infrequent. The cholinesterase may begin to climb or it may fall slowly. Then it fluctuates for a long period of time in the subnormal range despite proper rest and a good dietary intake. When this occurs, one should suspect incomplete hepatic repair or smoldering infection. (4) In the rare instances of severe and acute hepatic failure a precipitous drop in cholinesterase may be seen. The fall in cholinesterase may indicate fulminating hepatitis some days before clinical signs of failure are present.

The changes in cholinesterase activity seen in acute hepatic disorders are usually more dramatic than those seen in chronic liver disease. In acute liver disease serum cholinesterase does not reflect the nutritional status of the patient; its ups and downs are related to the extent and degree of damage to the hepatic parenchyma.

Nutritional bankruptcy usually accompanies chronic liver disease, especially in cirrhosis with alcoholism. Here we suspect that low cholinesterase levels may sometimes be the product of hepatic cell damage and nutritional dysfunction. When cirrhotic patients are rehabilitated with high protein diet therapy, sometimes the improvement in cholinesterase activity parallels weight gain, week by week and month by month,[41] but most often in cirrhotics there is no close relationship between weight gain or general improvement in nutrition and improvement in cholinesterase activity.[42]

Several investigators have observed the close correlation that exists between levels of serum albumin and serum cholinesterase.[27,45,46,48] We agree that both reflect the ability of the hepatic cell to synthesize protein; however, it appears that measurement of serum cholinesterase activity affords a better index of protein synthesis because of the wider range over which changes take place and because of the relatively inaccurate methods currently in use in most clinics for the determination of serum albumin concentration.

Malnutrition and Chronic Debilitating Diseases. In malnutrition serum cholinesterase activity is generally depressed. This does not tend to be as marked as that observed in liver disease although in rare instances there may be considerable depression of activity. Low levels have been found in blood from patients who were malnourished as a result of starvation, anorexia or debilitating disease,[26,27,33,40,57,63,85] and they have also been observed in experimentally induced malnutrition.[42] The depression in enzyme activity reflects both the extreme protein depletion and the undoubted impairment of hepatocellular function that accompanies cachexia and chronic debilitating disease. We have noted, as Milhorat observed,[57] that when patients with debilitating diseases are treated and rehabilitated the rise in their serum cholinesterase activity parallels the nutritional improvement and weight gain.[41] Figure 4 demonstrates clearly the relationship between malnutrition and serum cholinesterase in a patient ill with beriberi and shows the beneficial effect of adequate diet therapy.

In the patient with beriberi the cardiovascular manifestations were completely cured weeks before the serum cholinesterase returned to normal. In this patient and in other malnourished individuals the slow return of the enzyme seems to be related to restoration of tissue mass

and a positive nitrogen balance. We speculate that the cholinesterase level may be an index of the over-all protein economy of the body.

Acute Infectious Diseases. Several authors have observed mild to moderate depression of serum cholinesterase activity in a variety of acute infectious diseases.[3,21,26,33,35] We have noted the same tendency although the series is small and the spectrum of diseases studied is not broad. With cessation of the active disease process the cholinesterase spontaneously returns to normal levels. The depression in enzyme activity is mild, never as severe as in acute hepatitis, and is probably the result of impairment of liver function which accompanies the acute infectious process and which is perhaps due to hyperpyrexia and local anoxia. It is also possible that the negative nitrogen balance resulting from "damage" and the reduced protein intake occasioned by anorexia may play a part. However, preliminary studies in surgical patients showed no significant depression of serum cholinesterase in the *immediate* postoperative, protein-catabolic period of recovery.

Anemias. Many authors have commented upon the low levels of serum cholinesterase activity found in various types of anemias.[3,21,26,33,57,71–73] These include pernicious anemia, the anemia of sprue, Cooley's anemia, the acute hemolytic anemias, anemias secondary to blood loss, anemias associated with malignancy and leukemia, myelophthisic anemia and the anemia of chronic infection. It is intriguing that abnormal levels have never been found in patients ill with sickle cell anemia[73] or in our patients with acute hypoplastic anemias or polycythemia.

Serial studies of serum cholinesterase in anemias[79] have shown that the enzyme activity rises to normal levels as the disease is treated. In most instances this parallels the general clinical and nutritional improvement of the patient rather than the improvement in the blood picture *per se*. Moreover, inhibition of plasma cholinesterase by injection of di-isopropyl fluorophosphate during active hematopoiesis does not interfere with regeneration of hemoglobin and erythrocytes or the clinical improvement of the patient.

DISEASE STATES IN WHICH SERUM CHOLINESTERASE ACTIVITY IS NORMAL

There are a number of diseases and syndromes such as asthma, epilepsy and myasthenia gravis which may be related to abnormality of acetylcholine or serum cholinesterase metabolism because of their relationship to the autonomic or central nervous system. These are reported here together with other conditions in which serum cholinesterase activity is normal.

Myasthenia Gravis. Because the pathophysiology of myasthenia gravis is thought to be related to excessive amounts of tissue or serum cholinesterase, or insufficient quantities of acetylcholine, at the myoneural junctions, many investigators have studied serum cholinesterase activity in patients ill with myasthenia gravis.[33,48,53,57,66,81] All have found enzyme concentrations to be normal except Pichler, who found low levels in three patients,[65] and Hicks and MacKay,[37,38] who reported high levels in five patients. Four patients with myasthenia gravis were studied intensively while their muscular weakness was controlled with prostigmine and also during relapse when therapy was withheld. Normal levels of cholinesterase were found in all four patients throughout the study, and the increasing muscular weakness following prostigmine withdrawal was not reflected by changes or fluctuations in cholinesterase activity.

Bronchial Asthma. One hypothesis which has been advanced to explain the pathophysiology of bronchial asthma suggests that an imbalance of the autonomic nervous system may play a role in the disease. The autonomic imbalance could be produced by decreased activity in tissue or serum cholinesterase activity, or by an excessive liberation or production of acetylcholine in the blood flowing through the lungs.[19,25,59] Like a number of investigators[26,36,53,57,85] we noted normal enzyme activity in fourteen patients ill with bronchial asthma, including two patients who were studied during severe asthmatic attacks.[78] On the other hand, high levels of acetylcholine were found. This may have been the cause or the result of the bronchial constriction and needs further clarification.

Epilepsy. It has been suggested that in epilepsy low levels of serum cholinesterase may allow excess acetylcholine in the brain to initiate seizures. However, we doubt that this hypothesis is correct as normal levels of serum cholinesterase activity have been reported in patients suffering with epilepsy.[13,57] We have confirmed these findings in four epileptic patients although none were studied during convulsive episodes.

Hyperthyroidism. Several authors have reported high levels of serum cholinesterase activity in patients ill with hyperthyroidism.[3,30,39,53,85] Others have not substantiated these findings.[26,53,57] In view of the great loss of weight found in so many of these patients one would expect to find low levels of serum cholinesterase activity. We studied enzyme activity in eighteen patients suffering with thyrotoxicosis and found it to be within the normal range in every case. In this group of patients basal metabolic rates ranged from +20 to +70 per cent of normal. No correlation was found between loss in body weight or the degree of elevation of the basal metabolic rate and the level of serum cholinesterase activity. Serial studies on two patients under therapy with propylthiouracil failed to demonstrate any changes in normal enzyme concentration as the patients were restored to a euthyroid state.

Hypertension. Elevated levels of serum cholinesterase have been observed in patients ill with hypertension[3,26,62] and it has been suggested that there may be a relationship between enzyme activity and the height of blood pressure.[61,62] These findings have not been substantiated by other investigators[13,35,53,57,68] who found normal serum cholinesterase levels. We have studied enzyme activity in sixty-three hypertensive subjects and found no abnormalities in this group of patients. Several of these patients were treated with a number of drugs and different therapeutic measures known or reported to affect either blood pressure or serum cholinesterase activity. These included tetraethylammonium chloride, vitamin K, folic acid, sodium amytal, di-isopropyl fluorophosphate, benzodioxane, veratrum viride, cold pressure tests and the rice diet regimen. No correlations were observed between fluctuations in blood pressure and enzyme concentrations.[88]

Diabetes Mellitus. In patients ill with diabetes mellitus some investigators[3,26,85] found levels of serum cholinesterase activity to be slightly higher than normal, while others have not confirmed this.[13,57] Seven diabetic patients were studied repeatedly while they were in the hospital. Two of these patients were considered to be suffering from the Kimmelstiel-Wilson syndrome. Administration of insulin to the patients did not influence the serum cholinesterase activity, which was consistently normal.

Other Diseases. Low levels of serum cholinesterase were observed in five patients ill with myotonia congenita by Hicks and MacKay[38] although others have not confirmed this.[26,66] We have not studied any such patients. Low levels of enzyme concentration have been reported in chronic nephritis[26,33] although no mention was made concerning the stage of the disease or the nutritional state of the patients studied. Others have been unable to confirm this.[53,57] We made determinations in only six patients with chronic glomerulonephritis and found no abnormalities in the cholinesterase activity of their sera. Normal levels of enzyme concentration were found in patients suffering with duodenal ulcer[13,53,85] and various cardiac arrhythmias.[13] Our observations in a small number of patients confirm these findings. Tod and Jones found low levels of serum cholinesterase in patients suffering with "anxiety-states"[83] but this observation has not been confirmed.[13,57] Normal levels of enzyme concentration were also found in small numbers of patients and in a wide variety of diseases which were studied in general hospital surveys.[3,13,26,35,53,57,85]

CONDITIONS IN WHICH SERUM CHOLINESTERASE ACTIVITY IS HIGH

Nephrosis. Elevated levels of cholinesterase in the serum of patients ill with the nephrotic syndrome have been found by several investigators.[16,26,28,33] Nineteen such patients, both adults and children, were studied on our service. In most instances the serum enzyme activity was extremely high. (Fig. 5.) On the other hand, although their urine was loaded with protein it contained no detectable amounts of cholinesterase.

We have presented elsewhere data[36] which suggest that the rate of synthesis of protein by the liver cell is determined in part by the level of circulating albumin. When this level is artificially raised above the normal concentration, the hepatic cells "rest" in a way which may perhaps be analogous to what is observed in the case of endocrine glands when hormones increase in the blood stream. When the serum albumin level falls, as it does in nephrosis, the liver may be stimulated to synthesize extra protein. On the basis of our observations we speculate that the high level of serum cholinesterase in nephrosis reflects an increased and possibly maximal effort of the liver to synthesize new protein. In nephrosis the loss of albumin in the urine drains both circulatory and extracirculatory albumin. The reduction in the

normal mass of the albumin pool stimulates the hepatic cells to produce more albumin to maintain osmotic equilibrium, but unfortunately, the relatively small molecules of albumin pass through the glomeruli and serum albumin levels remain low. The stimulus to the hepatic cell to produce more albumin also calls forth from it a parallel abnormally high rate of synthesis of serum cholinesterase. However, the cholinesterase molecule is over twice the size of the albumin molecule. It does not pass through the glomerular membrane and is not dissipated in the urine. These speculations provide a rational explanation to account for both the low level of albumin and the high level of cholinesterase in the blood of nephrotic patients.

Three of our patients ill with the nephrotic syndrome received ACTH therapy and in two of them (both children) enzyme concentrations fell to normal levels. The third patient, an adult, did not improve with ACTH (160 mg. daily for ten days) or with cortisone therapy (100 mg. daily for ten days). Serial studies of her serum cholinesterase activity showed no change. We have no explanation for these phenomena.

Exercise. Croft and Richter[18] reported that vigorous muscular exercise of short duration (four to twenty-five minutes) caused a temporary rise in serum cholinesterase which returned to normal after rest. They claim that the rise in serum cholinesterase is the result of a shift of cholinesterase from the erythrocytes to plasma. To our knowledge, these observations have not been repeated by other investigators. It is quite possible that the increase in cholinesterase after exercise reflects changes in blood volume, which Croft and Richter did not measure.

DRUGS AFFECTING SERUM CHOLINESTERASE ACTIVITY

Many drugs have been found to affect the level of the serum cholinesterase activity, some increasing its concentration, others acting to decrease it. It is surprising, however, that acetylcholine, even when administered in large amounts over prolonged periods of time, is without effect on the enzyme concentrations in the serum.[34,57] The practical value of measurement of serum cholinesterase in the study of drugs is demonstrated by the recent observations that some insecticides in common use, such as octamethyl-pyrophosphonamide or other organo-phosphono compounds, depress serum cholinesterase activity in persons exposed to these substances.[96] Single and serial measurements of cholinesterase in people exposed to or using these insecticides can readily screen out those who have been poisoned. Thus measurement of serum cholinesterase may be a useful

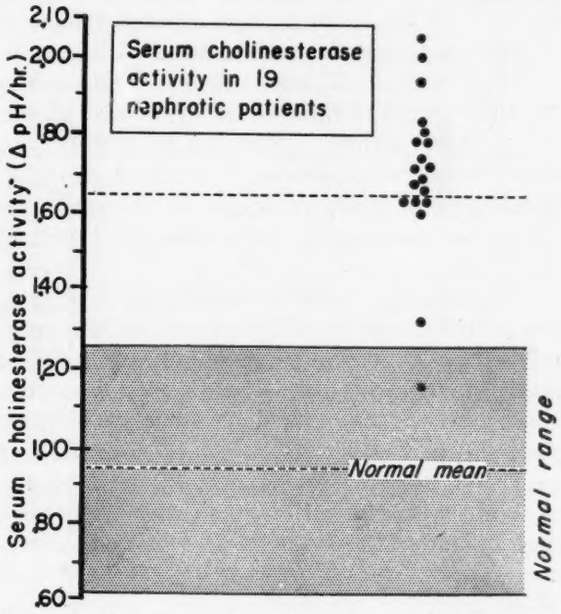

FIG. 5. Scattergram showing serum cholinesterase activity in the nephrotic syndrome. Each point represents one patient; dotted line indicates mean value.

method of survey for public health authorities or others concerned with the control of health.

Drugs Which Increase Serum Cholinesterase Activity. We have given nitrogen mustard by vein to three patients ill with Hodgkin's disease and to one patient suffering with chronic leukemia. In all patients slow progressive rise in enzyme activity followed treatment and this continued for about three weeks. In two of the patients there was 100 per cent increment in activity, the cholinesterase rising from 0.53 ΔpH /hr. to 1.08 ΔpH/hr., and from 0.31 ΔpH/hr. to 0.7 ΔpH/hr., respectively. No change in cholinesterase activity was seen in a patient ill with Hodgkin's disease who was treated with deep x-ray therapy, although it has been reported elsewhere that deep x-ray therapy is followed by reduction in whole blood cholinesterase.[9] The increase in serum cholinesterase after nitrogen mustard therapy is not the result of improvement in the general condition of the patients, as far as can be ascertained, but possibly reflects liberation of cholinesterase into the plasma from the breakdown of cells destroyed

by the drug. It is also of interest that several of the nitrogen mustards and related chemical vesicants have been reported to inhibit cholinesterase *in vitro* in the Warburg vessel.[49,82]

Insulin is said to cause a rise in serum cholinesterase activity when administered to schizophrenic patients to produce prolonged hypoglycemia.[67] We have noticed no such effects in diabetic patients who were treated with insulin.

Drugs Which Decrease Serum Cholinesterase Activity. A large number of drugs are known to decrease serum cholinesterase activity. In most cases the depression is of short duration although one group of drugs, the alkyl fluorophosphates, causes an irreversible inhibition of the enzyme.

The administration of vitamin K, folic acid, tetraethylammonium chloride and sodium amytal *in vivo* is promptly followed by a mild or moderate but temporary depression of the serum cholinesterase activity. These effects, which we have been unable to duplicate *in vitro*, are probably due to reversible inhibition of the enzyme by the drugs. Other drugs have been found to inhibit the activity of serum cholinesterase. The effects of physostigmine[47,70,85] and prostigmine[53,70] are well known. However, a wide variety of seemingly unrelated drugs also are effective in causing reduction of cholinesterase activity. These include quinine and atoxyl,[69,85] caffeine, theophylline and theobromine,[11] adrenaline,[8] strophanthin,[17,20] chloroform and ether,[60,84] d- and l-isomers of amidone and isoamidone,[32] antimalarial drugs (including chloroquine, quinacrine, plasmochin, quinidine, quinine and paludrine)[93] phenanthrene amino acids,[92] barbiturates, choline,[18] choline, arsenocholine, acetyl-beta-methylcholine, tetraethylammonium chloride, atropine, and d- and l-hyocyamine,[70] morphine,[22,91] desomorphine, codeine and dilaudid,[91] phenothiazine derivatives,[95] antipyrine and antipyrine derivatives,[23] procaine hydrochloride,[2] sulfanilamide and para-aminobenzoic acid,[94] atropine,[43,93] quaternary ammonium compounds[43] and thiamin.[31] Scorpion venom has also been found to be a weak inhibitor of serum cholinesterase.[23] The mechanism by which these various drugs act on the enzyme activity is not known. Possibly some of them, such as chloroform, may act to depress the hepatic synthesis of cholinesterase while others may inhibit the enzyme, inactivate it by a chemical reaction with it, or successfully compete with it for its substrate. Undoubtedly, the property of many of the aforementioned drugs to inhibit serum cholinesterase constitutes a relatively unimportant side action.[44]

Changes in serum cholinesterase activity observed following ACTH therapy in patients ill with the nephrotic syndrome have been described. We have estimated serum cholinesterase activity following administration of ACTH to patients with a variety of other diseases and have not observed gross changes in its concentration in any other case studied although mild depressions in enzyme activity have been noted in some cases of chronic ulcerative colitis following prolonged ACTH therapy.[7]

Effect of the Alkyl Flurophosphates, Particularly Di-isopropyl Fluorophosphate, on Serum Cholinesterase Activity. The alkyl fluorophosphates have been found to be extremely potent inhibitors of serum cholinesterase and the tissue cholinesterases.[50] Unlike the drugs previously mentioned, these compounds act to inhibit the enzyme irreversibly and the effects are of long duration. Of these drugs, the one that has been most extensively studied is di-isopropyl fluorophosphate (DFP).[51] Large doses of DFP may produce symptoms or signs of poisoning or kill by inhibiting cholinesterase in the central nervous system. Small amounts (0.02 mg. per kg.) given intramuscularly in oil cause no symptoms of ill health but they produce an abrupt and marked drop in serum cholinesterase activity which may exceed 95 per cent of the preinjection level.[33,45,89] Larger amounts can reduce the serum cholinesterase to zero. The subsequent rise in enzyme concentration reflects the rate of synthesis of new cholinesterase protein since, as already mentioned, all evidence indicates that the liver is the sole source of production of the enzyme molecule. As far as is known DFP is without effect on serum albumin, nor does it effect the other commonly used tests of liver function enumerated earlier in this article.

We have studied regeneration of serum cholinesterase activity following injection of DFP in sixteen individuals; these include healthy subjects and patients ill with cirrhosis, the nephrotic syndrome or other diseases. The regeneration of cholinesterase, when compared with normal, is less in patients with hepatocellular disease and greater in the nephrotics. The rate of regeneration varies directly with the preinjection level of cholinesterase; the higher the initial enzyme concentration, the steeper the curve of regeneration. Complete regeneration,

however, requires approximately twenty-eight days in all instances.

EFFECT OF INTRAVENOUS HUMAN SERUM ALBUMIN ON SERUM CHOLINESTERASE ACTIVITY

Daily administration of considerable amounts of intravenous salt-poor human serum albumin

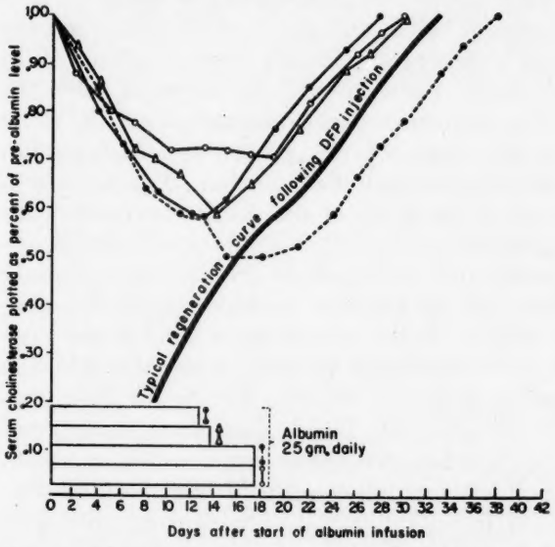
Serum cholinesterase plotted as percent of pre-albumin level
Typical regeneration curve following DFP injection
Albumin 25 gm. daily
Days after start of albumin infusion

FIG. 6. Changes in serum cholinesterase activity in four individuals during and after daily intravenous infusion of human salt-poor serum albumin (50 gm. per day), compared with a typical curve of regeneration after injection of DFP (di-isopropyl-fluorophosphate).

produces a steady slow depression in serum cholinesterase activity.[86] Twelve individuals studied on our service including healthy subjects and patients ill with cirrhosis of the liver all showed this effect. The enzyme concentration falls gradually but continuously during the period of albumin administration. (Fig. 6.) The higher the preinjection level of serum cholinesterase, the greater the fall in its concentration during albumin therapy. This depression is far greater than might be expected from the increase in blood volume (as determined by changes in hematocrit and in blood volume which was measured with Evans blue dye) that accompanies the albumin administration. Immediately upon cessation of albumin therapy the serum cholinesterase activity starts to rise again until preinjection levels are reached. In the individual patient the return to preinjection level of enzyme concentration takes as long as it took to depress the cholinesterase with daily albumin therapy, and the slope of the curve of regeneration is identical with the slope of the falling curve of cholinesterase activity during albumin administration. (Fig. 7.) Changes in cholinesterase activity were not found to occur with intravenous administration of amino acids or with other forms of intravenous therapy, nor do they appear when albumin is incubated with serum *in vitro*. The hepatic origin of serum cholinesterase protein has

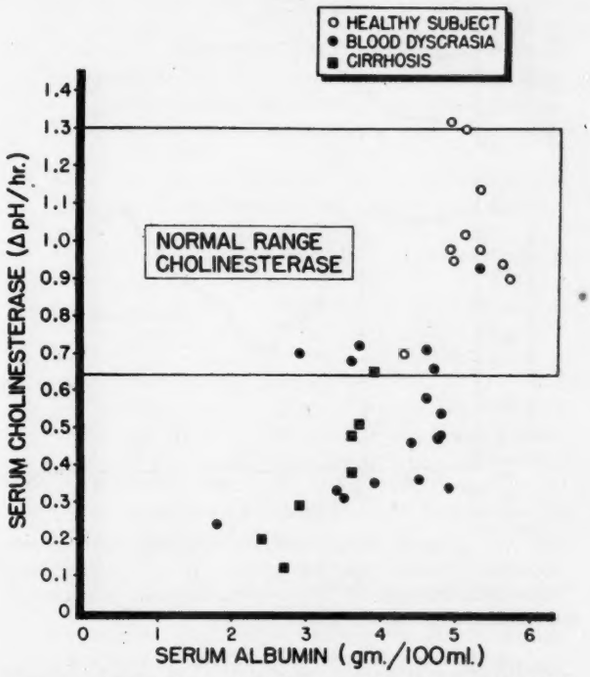

FIG. 7. Comparison of plasma cholinesterase activity with serum albumin levels in ten healthy subjects, in sixteen patients ill with various blood dyscrasias and in seven patients suffering with cirrhosis of the liver. (Scudamore, H. H., Vorhaus, L. J. and Kark, R. M. Observations on plasma and erythrocyte cholinesterase activity in dyscrasias of the blood. *Blood*, 6: 1260, 1951.)

already been mentioned. There has been much emphasis in the literature on the intimate relationship between serum cholinesterase and serum albumin,[27,45,46,48] and this is shown in Figure 8. We interpret the depressant effect of intravenous albumin administration on serum cholinesterase activity as further evidence of the hepatic origin of cholinesterase protein. All available evidence suggests that it is produced in parallel with the albumin molecule, and its synthesis seems to be stimulated or inhibited by factors which stimulate or inhibit albumin production. The intravenous infusion of human serum albumin causes an elevation in the level of circulating serum albumin which probably depresses the rate of hepatic synthesis of albumin. A parallel depression in cholinesterase produc-

tion would explain the drop in serum cholinesterase activity that we have observed under these circumstances. This concept of parallel synthesis of albumin and cholinesterase also explains the low levels of serum cholinesterase activity observed in liver disease, chronic

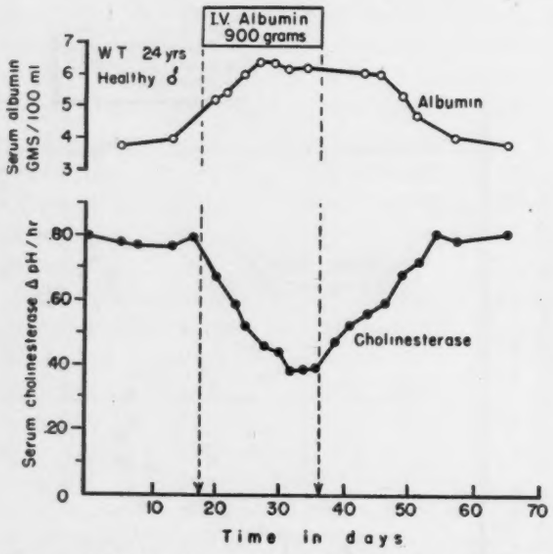

FIG. 8. Changes in serum cholinesterase and serum albumin levels in healthy subject, W. T., during and after daily infusion of 50 gm. of human salt-poor serum albumin each day for eighteen days.

debilitating diseases, malnutrition, acute febrile diseases and various anemias, in all of which albumin synthesis is probably depressed, and the high levels found in the nephrotic syndrome which were discussed previously.

LIFE SPAN OF THE CHOLINESTERASE MOLECULE

The depression of serum cholinesterase activity following administration of DFP has already been discussed and it has been pointed out that complete regeneration of serum cholinesterase activity requires approximately twenty-eight days in all cases, regardless of how steep or flat the curve of the regeneration may be. If the regeneration curves are plotted in terms of per cent of preinjection levels instead of actual values, the curves all become superimposable, with an identical slope. By using Schoidt's formula ([average daily rise during a definite period of time] × K [longevity] = [end value of regeneration] − [lowest value])[76] the life span of the molecule may be calculated to be twenty-eight days. Further evidence to support this calculation is obtained from the curves of cholinesterase activity during and after albumin administration. If the fall in enzyme concentration is due to cessation of hepatic synthesis of cholinesterase protein, this fall can be considered to be a decay curve, and the subsequent rise following albumin therapy a curve of regeneration. When these changes in serum cholinesterase activity following albumin infusion are plotted in terms of percentage of preinjection levels, the slopes of the decay curves and regeneration curves become identical in all cases. Furthermore, the slopes of both the decay and the regeneration curves are the same as the slope of the percentage regeneration curves following DFP injection. (Fig. 6.) Moreover, if the slopes of the decay curves are continued downward, they would reach zero in approximately twenty-eight days (actually slightly less, due to increase in blood volume); and, similarly, if the regeneration curves are continued downward to zero, a twenty-eight-day period would be required for the rise from zero to 100 per cent. This is the same time interval required from complete regeneration of serum cholinesterase following DFP injection and supports the calculated twenty-eight-day life span of the molecule. It is of interest that these observations compare favorably with studies on the albumin molecule in which, using radioactive isotopes, the half-life has been found to be about ten to fourteen days.[58,64,75]

SUMMARY

1. The origin, nature and function of the serum cholinesterase is discussed.

2. Values for serum cholinesterase activity in 120 healthy individuals, as determined by Michel's simple electrometric method, are presented.

3. Changes in serum cholinesterase activity are described in a variety of disease states. In general, low levels are found in patients ill with liver disease, malnutrition and chronic debilitating diseases, acute infectious diseases and anemias. Normal levels are observed in patients ill with uncomplicated obstructive jaundice, myasthenia gravis, hyperthyroidism, asthma, hypertension, epilepsy, diabetes mellitus and many other diseases. High levels occur in the nephrotic syndrome.

4. Changes in serum cholinesterase activity following administration of a variety of drugs are described.

5. Evidence is presented to support the concept that the serum cholinesterase molecule is

synthesized in the liver in parallel with the albumin molecule and that it has a life span of approximately twenty-eight days.

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Seminars on Blood Coagulation

An Evaluation of Anticoagulant Therapy*

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THROMBOEMBOLISM is a manifestation of a very large number of diseases with varying etiologies and affecting different portions of the vascular tree. It is axiomatic in medicine that any rational treatment must be based upon an understanding of the etiology, pathogenesis and mechanism involved in a disease state, yet these fundamentals have often been neglected in the consideration of thromboembolic conditions. Of perhaps equal importance is the anatomic location of a thrombus or embolus and its effect upon the circulation to local tissues. To be specific, a thrombosis in the splenic vein of a patient with polycythemia vera confronts the physician with a vastly different problem than a thrombosis in a varicose vein in the leg, a cerebral embolus arising from a mural thrombus from within a heart in auricular fibrillation, or a chemical thrombosis produced by a faulty or irritating injection in the vein of an arm.

High among the complications encountered on medical, surgical and obstetrical services of all hospitals one must rank thrombophlebitis in the veins near the sites of operation or malignant growths, or in the veins of the lower extremities. Once such thrombosis has been recognized, if suitable therapy is not undertaken there is nearly a 50 per cent chance that a pulmonary embolism of sufficient size to be recognized clinically will occur. Patients who have had one pulmonary embolus, if untreated, have a 20 per cent chance of death from subsequent pulmonary emboli. Some patients recover without apparent sequelae but there are literally thousands of individuals in the United States who are permanently partially disabled because of severe venous insufficiency with marked edema, often with painful and intractable ulceration. The serious embolic complications from mural thrombi formed within hearts which are in fibrillation or following myocardial infarction may include hemiplegia, gangrene of an extremity or a portion of intestine, as well as massive infarctions of the kidney, spleen, lungs and many less critical areas of the vascular tree. However benign a thrombosing process may appear, it is potentially capable of propagating until it is much larger, blocking out additional segments of veins and their collateral circulation or arteries and their branches. It is therefore essential that thromboembolic complications be regarded seriously from the viewpoint of prevention as well as treatment.

During the past ten years evidence has accumulated which has clarified the indications for anticoagulant therapy. Today anticoagulants are widely used for the following conditions: (1) Coronary occlusion with myocardial infarction; (2) rheumatic heart disease with pulmonary or peripheral embolization (usually associated with auricular fibrillation); (3) venous thrombosis (thrombophlebitis, phlebothrombosis); (4) thrombophlebitis migrans; (5) pulmonary emboli from a venous or an unrecognized source; (6) sudden arterial occlusion due to embolism or thrombosis; (7) chronic congestive heart failure with a tendency to develop thromboses; (8) a familial tendency to develop thrombosis which has manifested itself in the patient; (9) prophylactically, postoperatively; (10) in vascular surgery and (11) retinal vein or artery thrombosis.

It is now accepted that anticoagulants not only prevent the formation and propagation of clots but they actually aid in the disintegration or digestion of clots, probably by permitting freer action of enzyme systems in the blood.

The general contraindications are well known. Anticoagulants should be avoided or used with great caution only when the indications are strong, under the following circumstances: (1) Prothrombin deficiency (hypoprothrombinemia) due to vitamin K deficiency or severe

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liver disease; (2) blood dyscrasias with impairment of the normal mechanisms for hemostasis; (3) renal insufficiency; (4) vitamin C deficiency, until this is corrected; (5) surgical or accidental trauma to the brain or spinal cord or leaving wide raw and oozing surfaces; (6) ulcers, malignant or benign, especially of the gastrointestinal and urinary tracts and (7) subacute bacterial endocarditis.

It has been found necessary to use especial care in determining the dosage in combination with large doses of gut-sterilizing antibiotics, e.g., aureomycin, chloromycetin or terramycin. It also seems clear that the use of cortisone and similar compounds appears to encourage thrombosis in some patients and this tendency may constitute an indication for anticoagulant therapy as an adjuvant if it is considered important to continue cortisone therapy.

The Reports of the Committee on Anticoagulants of the American Heart Association, based on studies of 1,031 cases, clearly showed that the over-all death rate and, to an even greater degree, the thromboembolic complication rate from myocardial infarction could be reduced by the use of anticoagulants. The patients in this study were followed and analyzed in detail from the day of admission until the day of discharge, and the improvement in the results with the treated group was statistically significant when compared with the control group. Recently some workers have suggested that patients with mild or only moderately severe myocardial infarction may not hope to gain sufficiently by anticoagulant therapy to warrant the cost and effort involved.[1–3] In some instances, these conclusions have been based on a review of case histories not carefully compiled with such a study in view but only after the patients have recovered or died from their acute attack. Other conclusions have been based on cases seen only in consultation or at home. They do not correspond with the method of the Committee by which each patient was classified by the study team at onset as mildly, moderately or severely ill. The early hours represent the period when a physician, confronted with a patient with a pain in the substernal area and other evidences of infarction, should make his decisions regarding initial therapy if he wishes to exercise the most favorable influence on the course and outcome of the illness. As is seen in Tables I and II, delay might have serious consequences.[4]

In the study of the Anticoagulant Committee it was found that the borderline between mild and moderate ("good risk cases") was generally less well defined in the physician's mind than that between moderate and severe ("poor risk cases") so that the mild and moderate cases were grouped together. It will be seen that the death rate in the control groups for this "good risk" category was 12.9 per cent whereas the treated group had a death rate of only 7.9 per cent, a reduction of 45 per cent. Thromboembolic complications occurred in 22 per cent of the controls in the mild or moderate group but in only 8 per cent of the treated cases, a reduction of 64 per cent. Many patients who do not receive anticoagulants suffer from more than one complication. The number of thromboembolic complications per hundred patients was 34 for the "good risk" control group as against 9 for the treated group. These differences are highly significant statistically and *do not appear to justify the position that only severely ill patients with myocardial infarction should receive anticoagulant therapy.*

TABLE I
TREATMENT OF MYOCARDIAL INFARCTION WITH ANTICOAGULANTS—EFFECT IN RELATION TO SEVERITY AT ONSET*

Severity	No. of Cases		Percentage of Patients Dying	
	Control Group	Treated Group	Control Group	Treated Group
Mild or moderate at onset..	326	408	12.9	7.2
Severe at onset.	116	181	45.2	35.2
Total.....	442	589		

* Committee on Anticoagulants, American Heart Association.

Criteria were then used by which patients who had any of the previous complications listed in Table III on or before the day of admission were listed as "poor risk" cases. A selection was carried out among which there were no deaths in either the control or treated cases. These were classified as "good risk" cases. This reduces the group to approximately 17 per cent of the 1,031 patients in this study, certainly a highly selective process resulting in a small sample. It indicates that this "good risk" group

represents a small proportion of patients hospitalized for myocardial infarction in the sixteen participating hospitals. An analysis of embolic complications was made with the findings indicated in Table IV. Thus by the several methods of analysis used, the use of anticoagulants was shown to influence the outcome favorably even in very critical groups of "good risk" cases.

If physicians were endowed with prophetic insight on the first day of an acute infarction, it would be possible to decide without additional risk to the patient whether to give anticoagulants or not. The patients studied by the Committee on Anticoagulants were all hospitalized patients. There are undoubtedly many very mild cases of myocardial infarction in which anticoagulants cannot improve the outcome. The members of the Committee and their teams, well qualified though they were, failed, on the basis of the condition of the patient during the first day, to predict with certainty which patients would have an uneventful recovery and which patients would die, or develop thromboembolic complications with resulting hemiplegia, occlusion of an artery to a limb, serious pulmonary embolism or fatal secondary myocardial infarction. Waiting for the first complication to occur before taking prophylactic action is hazardous for the patient.

There should be no fixed routine. For many reasons a physician may decide not to administer anticoagulants to a specific patient but he should make his decision on the basis of carefully compiled and analyzed data.

Mention should be made of the extensive experience of Smith and his associates who have recently reported on 920 cases of acute myocardial infarction, of whom 189 received anticoagulant therapy.[5,6] He has emphasized the difficulties in attempting to predict the outcome on the basis of the condition of the patient early in his course. At the Henry Ford Hospital mortality from first infarctions in patients not treated with anticoagulants has been 21.7 per cent.

In Smith's series only one thromboembolic complication developed on the first day but

TABLE II

TREATMENT OF MYOCARDIAL INFARCTION WITH ANTICOAGULANTS—EFFECT IN RELATION TO SEVERITY AT ONSET*

Severity	No. of Cases		Percentage of Cases Developing Thromboembolic Complications		No. of Thromboembolic Complications per 100 Cases	
	Control	Treated	Control Group	Treated Group	Control Group	Treated Group
Mild or moderate	326	408	22	8	34	9
Severe	116	181	37	17	64	23
Total	442	589	26	11	42	13

* Committee on Anticoagulants, American Heart Association.

TABLE III

CRITERIA FOR GOOD RISK LIMITED CASES TO THOSE WITHOUT THE FOLLOWING

1. Previous myocardial infarction
2. Fourth degree pain, first week* (separate category for third degree pain only—see tables)
3. Fourth degree shock, initial (or on day of admission)
4. Cardiac enlargement prior to onset
5. Gallop rhythm, first week*
6. Congestive heart failure, initial or on day of admission (based on symptoms other than one degree liver enlargement), or positive in history
7. Auricular fibrillation, auricular flutter, any type of heart block, first week*
8. Maximum pulse 110 or more, first week*
9. Diabetes during the illness
10. Overweight 30 per cent or more
11. Previous history of:
    (a) Pulmonary infarction or embolism
    (b) Varicose veins in legs
    (c) Thrombophlebitis
    (d) Other thromboembolic phenomena
12. Other states predisposing to thrombosis:
    (a) Polycythemia, current
    (b) Cancer, current
    (c) Cerebral accident, aphasia, or hemiplegia when may have been due to cerebral embolus, current or in previous history

* When cases were admitted after the end of the first week of the illness, all symptoms occurring on, or before, the day of admission were used in classification, the schedules being examined when necessary for the application of this principle.

eight developed the second day and fourteen the third day. Auricular fibrillation developed in thirteen cases the first day but in twenty-five additional cases later, and numerous other complications developed after the first day. He raises serious objection to the method of attempting to treat only the severe cases and his present point of view regarding the use of anticoagulants is that of "continued recommendation for use in all cases of myocardial infarction treated by a careful competent internist, or in a hospital where there is a capable anticoagulant service unless some contraindication exists." His figures on the improvement in mortality and thromboembolic complications confirm the report of the Committee,[7,8] as do those from a steadily increasing list of workers who have had extensive experience with anticoagulants in this country and abroad.[9–17]

TABLE IV

PATIENTS DEVELOPING EMBOLI IN RELATION TO GOOD AND POOR RISK CRITERIA

	No. of Cases		Patients Developing Emboli			
			No.		Percentage	
	Control	Treated	Control	Treated	Control	Treated
Good risk cases*	24 (Deaths—0)	47 (Deaths—0)	4	0	16.7	0.0
Poor risk cases	418	542	56	30	13.4	5.5
All cases	442	589	60	30	13.6	5.1

* The *good risk* cases were selected on the basis of the criteria in Table III. There were no deaths in either the control or treated group. These groups constituted only 17 per cent of the patients admitted to the sixteen participating hospitals with a diagnosis of acute myocardial infarction.

There has been some hesitancy in the use of anticoagulants for the treatment of congestive heart failure, primarily because the early reports[18,19] were exploratory and not based on sufficient material to be conclusive. Recent studies by Griffiths et al.[20] have been more comprehensive and it now appears that anticoagulants should be given during the serious phases of failure when the thrombosing tendency is increased.

The need for hospitalization has been advanced as a reason for not undertaking anticoagulant therapy. Provided satisfactory laboratory facilities are available, hospitalization, while desirable for seriously ill patients, is no longer considered necessary, and today hundreds of patients are carried on home care while many others are on long-term anticoagulant therapy while they pursue practically normal lives. That this is entirely feasible has been demonstrated by our own experience with 228 patients treated on an outpatient basis for 65,824 days (180 years and 125 days). This experience will be published shortly in detail.[21] The discipline necessary on the part of the patient and his physician has been repeatedly emphasized.

The indications and many of the problems of anticoagulant therapy have been clarified with the use of heparin® and dicumarol® (bishydroxycoumarin). Neither of these is a completely satisfactory anticoagulant although in skillful hands their use is not fraught with excessive risk. Throughout the past decade an intensive effort has been made to develop and to evaluate new anticoagulants which more closely fulfill ideal criteria, which include low toxicity, rapid therapeutic effectiveness following oral administration and low cost.[22]

Of the new substances affecting the prothrombin time tromexan® has been used most extensively here and abroad.[23] A comprehensive and comparative study has been conducted under the auspices of the second Committee on Anticoagulants of the American Heart Association and reported by Scarrone, Beck and Wright.[24] This study included observations on 514 patients with a variety of thromboembolic conditions (51 per cent myocardial infarction; 17 per cent thrombophlebitis; 8 per cent pulmo-

nary infarction, and miscellaneous groups). Responsible investigators in seven leading hospitals participated in this study. (Table v.) One hundred eighty-one patients were treated with dicumarol for a total of 5,006 days and 288 patients were treated with tromexan for a total of 6,643 days. This experience appeared to justify some conclusions. These were as follows:

TABLE V

THE SECOND COMMITTEE ON ANTICOAGULANTS OF THE AMERICAN HEART ASSOCIATION

PARTICIPATING HOSPITALS AND RESPONSIBLE INVESTIGATORS

Hospitals	Investigators
Bellevue Hospital, New York	E. Hugh Luckey, M.D.
Henry Ford Hospital, Detroit	R. Janney Smith, M.D.
Jackson Memorial Hospital, Miami	E. Sterling Nichol, M.D.
Lakeside Hospital, Cleveland	Harold Feil, M.D.
Mayo Clinic, Rochester	Nelson W. Barker, M.D.
Pennsylvania Hospital, Philadelphia	Joseph B. Vander Veer, M.D.
The New York Hospital, New York	Irving S. Wright, M.D.

Consultants

Ralph S. Overman, PH.D.

Grafton E. Burke, M.D.

Central Laboratory

Irving S. Wright, M.D., Chairman of Study

Louis A. Scarrone, M.D., Coordinator

Dorothy F. Beck, PH.D., Statistician

1. Previous reports that a more rapid initial prolongation of prothrombin times can usually be achieved with tromexan than with dicumarol have been confirmed. This characteristic makes it possible to protect the patient more rapidly with tromexan than with dicumarol in the initial stages of anticoagulant therapy when the risk of thromboembolic complications is usually especially high, as well as after a lapse in therapy when a rapid return to therapeutic levels is indicated.

2. Previous reports that prothrombin times usually return more rapidly to normal after the cessation of tromexan than after cessation of dicumarol have been confirmed in a variety of circumstances. This characteristic of tromexan is of advantage when it becomes advisable to terminate therapy, as when excessively prolonged prothrombin times, with or without bleeding, develop or when emergency surgery becomes necessary.

3. The power of the two anticoagulants to protect the patient from thromboembolic complications appeared about equal, as demonstrated by the close similarity in the thromboembolic complication rates for days of therapy under each of the two anticoagulants.

4. Fourteen autopsies were studied in detail. These did not reveal any difference in the toxicity of the two anticoagulants or in their effectiveness in preventing thromboembolic complications.

5. These studies suggest that, when given in single daily doses, tromexan is slightly more difficult to control than dicumarol. When the daily total is divided into two or three doses, the prothrombin time is more satisfactorily controlled.

6. In this series of patients two deaths occurred in which tromexan was probably implicated. In one of these poor control of prothrombin times played a role. Two deaths occurred in patients who received a combination of paritol® and dicumarol therapy. The clotting times were prolonged in both and the prothrombin times were 54 and 22 seconds, respectively. It is difficult to assay the part played in these latter deaths by each of the two anticoagulants involved.

7. As with all coumarin derivatives and phenylindanedione, the prothrombin times of patients receiving tromexan should be watched with especial care until the response pattern is fully evident. Thereafter the use of anticoagulants also requires meticulous supervision by the attending physician.

8. These foregoing conclusions related to the total experience with tromexan and dicumarol when employed in a variety of thromboembolic conditions in this study. In addition, some comparisons were possible with the findings of the previous study of the use of dicumarol in myocardial infarction.[4,7] Such comparisons require, however, the omission of patients with diagnoses other than myocardial infarction. These omis-

sions reduce the sample to 262 patients, of whom 139 received tromexan only; 106, dicumarol only; and 17, both anticoagulants. The following conclusions pertain only to this component of the total sample:

(*a*) Of the myocardial infarction patients receiving dicumarol only, 14.2 per cent died within six weeks of the date of onset as compared with 10.8 per cent of the patients receiving tromexan only. Since two of the dicumarol deaths occurred in association with the combined use of paritol and dicumarol, and since slightly more of the tromexan cases were mild at onset, and for other reasons, these differences cannot be attributed to differences between the two anticoagulants. Both death rates are slightly below the 16.0 per cent record of deaths within six weeks in the treated group in the previous dicumarol study, and substantially below the 23.4 per cent of deaths occurring in the control group in that study.

(*b*). The thromboembolic complication rates for the myocardial infarction patients were similarly favorable when compared with the results of the previous dicumarol study. During tromexan therapy in the present study thromboembolic complications averaged 2.3 per thousand days of therapy; during dicumarol therapy, 2.2 per thousand days. These day rates are both about one-third lower than the corresponding rate of 3.1 complications per thousand days during the period of dicumarol therapy in the previous study and significantly below the 12.7 rate per thousand days for the control group in that study during days of their illness corresponding to the period of therapy for the treated group.

(*c*). Thus the power of protection of the two anticoagulants in myocardial infarction does not differ greatly. When judged by comparison with the control group of the previous study, both produced significant reductions in death rates and in the incidence of thromboembolic complications. The experience of this study with an additional 262 patients with myocardial infarction therefore constitutes further confirmation of the major conclusions of the original study.

Since tromexan is about one-fifth as potent as dicumarol, the dosage is about 5 times as great, but this produces no problem since the total quantities are small. The first dose is usually 1,500 to 1,800 mg., subsequent daily requirements from 300 to 900 mg. divided into two or three doses. Rarely patients have been encountered requiring as much as 2,400 mg. per day for long periods.

Cyclocumarol (*Compound 63, B.L. 5, Cumopyran®*). No comparable study has as yet been carried out with cyclocumarol. Reports regarding this substance have appeared from several groups of workers.[25–28] Cyclocumarol acts like dicumarol and tromexan in that it depresses the prothrombin activity. It is two to three times as potent as dicumarol so that the average dosage requirement is less, but individual response varies so that the actual daily dose must be controlled by frequent prothrombin time determinations as with dicumarol and tromexan. Therapeutic levels may be obtained in twenty-four hours and are reached in the majority of patients within seventy-two hours.

The action of cyclocumarol is more prolonged than that of dicumarol, continuing five to fourteen days after therapy is discontinued. This may be regarded as an advantage in that three or four doses may be sufficient to maintain a therapeutic level during a week. It may be a disadvantage if one wishes to terminate the anticoagulant action quickly, especially since the water-soluble vitamin K preparations are frequently found to be relatively ineffective against the action of cyclocumarol. Vitamin K_1 in oral doses of 250 to 500 mg. is very effective, usually within eight hours, but this preparation is still very expensive and not in common use. There is no conclusive evidence that in therapeutic or excessive doses cyclocumarol is either less or more apt to produce bleeding than dicumarol or tromexan. When administered skillfully, it is an effective anticoagulant which may be used without undue risk.

The first dose is usually 100 to 150 mg., after which the average dose is from 25 to 75 mg. It has been suggested that additional doses should be given only when the curve of prothrombin time is showing a downward trend. Desirable therapeutic prothrombin levels should be maintained between 25 and 40 seconds (with a control of 15 seconds).

Phenylindanedione.® In 1944, Kabat, Stohlman and Smith[29] described the effect of certain indanedione derivatives on prothrombin levels in animals. Soulier and Gueben[30] (1947) reported the use of phenylindanedione clinically as an anticoagulant. Jaques[31] stimulated further interest in this substance by demonstrating that

its effect on the prothrombin time was more prompt than that of dicumarol.

Blaustein and his co-workers[32] have reported clinical experience with phenylindanedione. They have found that the most satisfactory initial dose was 200 mg. given orally for those patients weighing 150 pounds or more and 150 mg. for lighter patients. Following this dose a satisfactory therapeutic level (approximately 30 per cent of normal prothrombin activity) was reached in thirty-eight of fifty-three patients within thirty-six to forty-eight hours. In eighteen of these the therapeutic level was reached within twenty hours. In a few, however, there exists practically a complete resistance to this drug. In a series of 200 cases treated with phenylindanedione Blaustein encountered ten such patients.

As with all coumarin derivatives, relative resistance may be encountered but anticoagulant effect is usually noted with the prothrombin time test performed with 12.5 per cent plasma even with a delayed rise in the whole plasma test. With phenylindanedione, however, valuable time may be lost before its ineffectiveness is recognized.

Phenylindanedione quite frequently produces wide swings in the prothrombin time curve—even to prothrombin times of infinity. Nevertheless, bleeding has been rare with this drug. Divided doses totaling 50 to 140 mg. a day, depending on the requirements, result in a more stabilized curve. Toxic effects thus far reported include mild hematuria and epistaxis. Renal damage (believed by Soulier and Guegen[30] to be due to deposition of crystals in the tubules), dryness of the mouth, polydipsia, polyuria and tachycardia, and scarlatiniform rashes have followed dosage as high as 10 to 20 mg. per kg. per day but have not been observed by Blaustein with clinical dosage.

Phenylindanedione has the advantage of rapid cessation of action after eliminating the drug. The average time for return to normal of the prothrombin time is forty-eight hours.

Clinically the drug appears to be effective in the treatment of thromboembolic conditions although no large well controlled series has been analyzed as yet.

At the present reading phenylindanedione would appear to have the advantages of rapid action and cessation of action to a degree comparable to tromexan. Further studies with this drug are indicated.

Heparin. Heparin, first discovered by McLean,[33] has enjoyed widespread use as an anticoagulant for more than twelve years. Its use has been reported in detail in many papers and has been reviewed in detail by Jorpes[34] and by Marple and Wright.[35] The action of heparin is primarily antithrombin in nature. With the more widespread use of the coumarin compounds and phenylindanedione the indications for heparin have been somewhat modified and may be considered largely when anticoagulant action is desired immediately or within twenty-four hours, such as: (1) Immediately following embolization from whatever cause to reduce the risk of additional propagation of the mother clot and hence the risk of further emboli; (2) massive or recurrent coronary thrombosis with myocardial infarction; (3) extending or fulminating thrombophlebitis with or without emboli. In these conditions a coumarin compound is now usually started at the same time and as the effect on the prothrombin activity reaches therapeutic levels the heparin is discontinued.

In addition, heparin is now used quite generally in vascular surgery and, to a somewhat lesser degree, following cardiac surgery. It is thus far the most satisfactory anticoagulant acting primarily on the clotting time of the blood. It is, however, not without risk and must be administered with care and control by means of clotting time tests. These tests may be most inaccurate unless done with great care. Dosage and methods of administration have been discussed in detail elsewhere.[35] It should be mentioned that heparin is effective only when given parenterally and that a recent report[36] regarding its efficacy when given sublingually has been found to be in error.[37] It is difficult to prepare and it is expensive; therefore, substitutes have been sought. Of these paritol has been studied in greatest detail.

Paritol. Paritol, a synthetic polysulfuric acid ester of polyanhydromannuronic acid, is similar to heparin in both chemical structure and action. During the past four years studies have been carried on regarding its pharmacology, toxicology and clinical effects.[38–41]

Extensive clinical experience with this interesting material appears to justify the following conclusions: Paritol produces a significant prolongation of the clotting time when administered to humans. By adjusting the dosage this can be in the same range as following the administration of heparin. Paritol is about one-seventh as active as heparin when compared mg./kg.

The duration of the anticoagulant effect of paritol is from two to four times that of heparin. Repeated doses of paritol given at eight- to twelve-hour intervals can produce a satisfactory curve of the clotting time for anticoagulant therapy. The prothrombin time is also prolonged to a moderate degree in a range comparable to that observed with heparin therapy.

Certain adverse reactions have occurred in a sufficient number of patients to justify withholding recommendation of this substance for general use at present. The most important of these has been a shock-like reaction producing generalized vasomotor collapse in some patients. Adverse effects of lesser importance include elevation of the blood urea nitrogen in patients with renal disease, urticaria-like reactions and alopecia occurring weeks after administration in some patients. It should perhaps be recalled that the use of the early preparations of heparin was associated with severe reactions. If the undesirable reactions can be eliminated, paritol will represent an advance in that it is much less expensive to prepare and its action is more prolonged than heparin. It is presently very satisfactory for certain kinds of investigation in which an anticoagulant is desirable, as in some types of animal surgery or physiologic studies.

Treburon.® Treburon (a polyhexuronic acid derivative), the sodium salt of sulfated polygalacturonic acid methyl ester methyl glycoside, also has anticoagulant properties similar to heparin. Studies of its action and its use in animals and man have been recently reported.[41–44] Treburon has been found to have approximately one-third of the anticoagulant potency of sodium heparin and the dosage for intravenous use is therefore about three times that of sodium heparin, e.g., a dose of 150 mg. of treburon would be used in place of 50 mg. of heparin, etc.

Treburon can be given intramuscularly in doses of from 500 to 650 mg. When given intravenously the action, like that of heparin, is evidenced by prompt prolongation of the coagulation time which lasts for an average of three to five hours. When given intramuscularly the maximum effect is obtained in from three to six hours and a prolongation of the coagulation time may persist for from ten to over twenty hours. Hirschboeck et al.[44] report maintaining patients in satisfactory states of hypocoaguability for five days or more by the administration of treburon at twelve-hour intervals intramuscularly. While the primary action is as an antithrombin, treburon may also produce a considerable effect on the prothrombin activity. Therefore both Lee-White coagulation tests and prothrombin time tests are of interest although therapy can be controlled by using only the former. No effect has followed the oral administration of up to 2,000 mg. Protamine sulfate may be used to neutralize the effects of treburon in doses of 1 mg. of protamine for each 3 mg. of treburon but, as with heparin, the results are often unpredictable. Whole fresh blood transfusions are probably more reliable for this purpose.

We have been unable to learn of any immediate shock-like reactions following the use of treburon. Serious diarrhea has been encountered. Late alopecia has occurred in rare cases. No anticoagulant can be administered without some risk of hemorrhage, especially in patients in whom a blood dyscrasia or potential bleeding surface exists, and treburon is not an exception to this. Renal disease constitutes an indication for special caution in the use of treburon since the large molecules of treburon tend to be deposited temporarily in the renal tissues during intensive excretion. Greater experience will demonstrate whether the risk of its use varies from that of the comparable anticoagulants, heparin and paritol. This substance must be more completely evaluated before it can be safely made available for general clinical use.

Crystalline Trypsin.® Recently crystalline trypsin given intravenously has been used in the treatment of thromboembolic conditions by Innerfield, Schwartz and Angrist.[45,46] They reported that under controlled conditions of infusion rate, enzyme concentration and dosage, the intravenous administration of trypsin is safe and feasible in rabbits and dogs, that large trypsin doses *in vitro* and *in vivo* have powerful anticoagulant effects and that intravenously administered trypsin induces lytic effects upon artificially formed intravascular thrombi in rabbits and dogs. They stated that they did not find that small doses of intravenous trypsin hastened the clotting time in normal animals as Tagnon[47] had found in a previous study with hemophiliac patients. Nor did they find that intravenous trypsin predisposed toward intravascular thrombosis.

Animal studies by Taylor[48] in our laboratory, using intravenous lyophilized crystalline trypsin (enzar®) in rabbits, fails to confirm their claims but does confirm the work of Tagnon. Approximately 50 per cent of our rabbits have died during or after the administration of trypsin

(enzar) in doses ranging from 15 mg. in 10 ml. saline to 100 mg. in 200 ml. saline. By slowing the rate of administration and by increasing the dilution of enzar it is usually possible to increase the total dosage but even then the fatal dose is unpredictable in many animals. The majority of those dying pass through a brief convulsive state prior to death. Autopsies performed immediately have shown antemortem clots in the right side of the heart. In addition, hemorrhages have been found in the myocardium, and lungs, and retroperitoneally. Adherent clots have been found in the right side of the heart in all animals dying before the dose producing incoagulable blood is reached. This dose is approximately 40 mg./kg. and as it is approached the clotting time becomes progressively prolonged. Death at this concentration is more frequently associated with myocardial and pulmonary hemorrhages and less frequently with intracardiac clots. Kellner[49] has found areas of focal necrosis involving the striated muscles, especially the myocardium and diaphragm, in most of these rabbits.

Ormond and Knight[50] have given intravenous trypsin (enzar) in doses of 200,000 units (100 mg.) in 500 ml. of isotonic saline to nine patients. Six of these patients developed thromboses in a total of eleven veins into which infusions had been given. One patient with a thrombophlebitis developed signs and symptoms suggesting pulmonary embolism on the third day after the intravenous trypsin treatment. Innerfield et al.,[45] however, report having given very dilute crystalline trypsin intravenously to 101 patients with an occasional mild chill as the only untoward reaction.

It is doubtful whether these very dilute solutions of trypsin (enzar) which have been given to man without serious results and which fail to produce any measurable effect on the clotting time, prothrombin time, factor V concentration, antithrombin titers and fibrinogen levels have any therapeutic value. There are no conclusive studies on this most significant point. Pending more extensive, well controlled studies it would not appear justified to release this substance for general clinical use at present.

SUMMARY

1. During the past decade the indications for anticoagulant therapy have been clarified. They are listed herein.

2. In view of the reduction in both death rate and in the incidence of thromboembolic complications following coronary thrombosis with myocardial infarction with the use of anticoagulants in mild and moderately severe cases, the position that their use should be reserved solely for those patients who are severely ill at onset does not appear justified. This because, despite apparent mildness during the first day or two of the disease, the future course is difficult or impossible to predict with certainty and because the first complication may produce death, more serious illness or permanent disability.

3. Recent evidence favors the increased use of anticoagulants during more severe periods o congestive heart failure.

4. Newer anticoagulants are now rapidly being developed which generally can be classified as acting similarly to heparin or to dicumarol.

5. The clinical facts regarding each of the better known anticoagulants, including their advantages and disadvantages, have been outlined.

6. More complete experimental studies should be carried out before crystalline trypsin should be released for general clinical use.

7. The final decision whether to use anticoagulants or not, and which ones to use in a specific patient, must rest with the physician responsible for his care.

8. Among the important factors to be considered in making this decision are: (1) The diagnosis and condition of the patient; (2) the presence of any coincidental problem requiring caution or contraindicating their use; (3) the sound evidence indicating anticoagulant therapy under these particular circumstances; (4) the qualities of the specific anticoagulants under consideration; (5) the availability of accurate prothrombin and coagulation time tests; (6) the availability of vitamin K and K_1, and transfusions for emergency use; and, perhaps of greatest importance, (7) the conscientiousness, and skill in this particular field, of the physician who is responsible for their use.

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Clinic on Psychosomatic Problems

Anaclitic Treatment in a Patient with Ulcerative Colitis

THESE cases are chosen to illustrate the relation between psychiatric and medical factors in the production of symptoms. They are part of the Harvard teaching on the Psychiatric Service of the Massachusetts General Hospital. These psychiatric conferences are edited by Dr. Stanely Cobb.

DR. PETER E. SIFNEOS: The patient, an unemployed tree surgeon, is thirty-six years old. In September, 1951, he was admitted for the ninth time to the Massachusetts General Hospital because of a severe depression of two months' duration.

His present illness dates back to 1946 when, after the sudden death of his stepfather, the patient began having seven to eight bloody bowel movements daily. After two months he was admitted with the diagnosis of acute ulcerative colitis. He was treated medically and then, because of marked emotional instability, was transferred to the psychiatric service. After his discharge to the outpatient department, he received extensive psychotherapy for four years. During this time he was readmitted six times because of exacerbations of his ulcerative colitis Between attacks, however, he was able to do his work adequately.

In 1951 perineal abscesses developed and his bloody diarrhea increased. He was admitted in March of that year for the eighth time. The patient was acutely depressed apparently because his psychotherapist had left the hospital. Although he was given a new doctor, he failed to improve. He lost 40 pounds and finally underwent an ileostomy with subtotal colectomy. There was improvement postoperatively, with a 10-pound weight gain. Following discharge the patient was seen in the outpatient department three times weekly. Soon, however, he became depressed again. He was unable to work, and began having threatening auditory hallucinations. Voices often told him to jump in front of trucks. He started to drink but was unable to "drown the voices with alcohol." During this time he maintained an adequate weight and was not bothered by his ulcerative colitis. His suicidal and, at times, homicidal ideas, however, increased in intensity. In September, 1951, he was readmitted to the hospital.

The chief features in his mental status on this admission were: profound depression with suicidal ideas; motor agitation with marked tremulousness, fragmented stream of talk, preoccupation with threatening visual and auditory hallucinations, poor judgment and insight, but intact memory and orientation.

Physical examination revealed a thin, malnourished man with carious teeth. Hard, rubbery inguinal nodes were easily palpable. An ileostomy and an old rectus scar on the left side were present. There was pustular eruption of his face and abdomen with septic foci discharging serosanguinous material around the anal region.

Neurologic examination revealed no abnormality. Laboratory tests showed a hemoglobin of 11 gm. per cent with 8,000 white blood cells. The urine was negative.

There were three people in the patient's immediate family. His father, a "kind and affectionate" man, died of tuberculosis at a young age. His mother, alive and well at sixty-seven, is described variously: "domineering and snappy," "cold as a snake," and "terrible tempered." She never visited the patient while he was in the hospital. The older sister, thirty-nine years old, is the mother's favorite. The patient envied and fought with her constantly.

The patient was born in 1915. He is said to have been a feeding problem and to have had attacks of diarrhea until he was about four. They caused his mother a good deal of trouble. Toilet training at one and a half, however, proceeded without difficulty. When the patient was about three, his father developed miliary tuberculosis. The patient remembers him "vomiting blood and suffering terribly." When his father died, the patient was very depressed. The family moved

to the maternal grandmother's home. She was very fond of her young grandson. A few months later the mother remarried. Her husband disliked the boy intensely. He maltreated and beat him frequently and mercilessly. To please her husband the mother dressed her son in girls' clothes. When he was nine, his grandmother died unexpectedly. He remembers crying and wanting to "jump into her grave and stay with her forever." That year, too, although his work had been good, the boy was taken out of school and was put to hard manual labor by his stepfather. He did well and earned considerable amounts of money. The stepfather was pacified. On the day when the patient was thirteen, his stepfather took him to the cellar and offered him liquor. They both got drunk. The occasion, the patient feels, was the turning point in his life: it was the beginning of his very friendly relationship with his stepfather. He continued working hard and earning large sums of money. The stepfather was delighted.

When he was twenty-one, the patient married a mentally deficient women whom he had made pregnant. In the next nine years she presented him with nine children. Three of them had been fathered by other men. The patient's married life was a nightmare. His wife was incapable of taking care of a house and spent money carelessly. The patient provided adequately but his family lived in poverty and filth.

Despite threats from the church, community agencies and the police, the patient left his family when he was twenty-nine. He has never returned to them. He went to live with another married woman who was in love with him. She soon divorced her husband and gave the patient two illegitimate children: one mentally deficient boy and one girl. The patient continued working hard and earning well. He not only supported his new family but also began giving money to his mother and stepfather. When his stepfather died in 1946, the patient developed acute ulcerative colitis. He was treated for the next five years at the Massachusetts General Hospital.

When he was admitted for the ninth time, in 1951, complaining of a profound depression, he was placed in the restricted part of the psychiatric ward under suicidal precaution.

His physical condition was poor. He began discharging blood and pus from his rectum and from a septic area around his anus. After several weeks, in November, 1951, he underwent a combined abdominal perineal resection of the sigmoid and rectum under general ether anesthesia. After an uneventful postoperative period the patient returned to the psychiatric service.

Although he was given medication for his "constant pain," the patient found no relief. One month after the operation he was receiving 50 mg. of demerol every four hours with three extra 50 mg. doses at night (a total of between 450 and 500 mg.). He was also given 200 mg. of seconol. Despite penicillin intramuscularly and bacitracin ointment, the septic area in his perineal region continued to drain.

In December, 1951, the patient's second psychotherapist was called into the Army. His third, and present one, found the patient with mood fluctuations, threatening auditory hallucinations, complaints of severe pain, demands for extra medication and impulsive behavior that necessitated constant observation. The patient was discouraged about his progress and hostile to his new therapist. He did not want to "start all over again."

A new approach to the patient was necessary. Insulin and electric shock were contraindicated medically. Psychoanalysis was impractical. A last report, anaclitic (Gr. to lean on) treatment, was practicable and appropriate to the patient's needs.

This therapy, it was hoped, would help the patient's inability to trust people emotionally. Having seen the people to whom he had been attached (father, grandmother, stepfather and two therapists) die or "desert" him, the patient was afraid that either he would hurt (perhaps kill) or would be hurt by anyone to whom he attached himself.

The plan was to satisfy all the patient's desires, possibly for the first time in his life, and thus to convince him that he could depend upon and trust his therapist completely. Then, while he was being constantly assured, by interpretation and continued interest, of his therapist's good will, the patient would be slowly restricted in his privileges and would be encouraged to become self-reliant.

Satisfying all the patient's desires was difficult: he asked for large amounts of medication and alcohol; he ate special foods and he demanded a great deal of time and reassurance from his therapist.

His reaction to his first satisfaction, medication, was immediate. He became friendly with his therapist and talked freely in his interviews.

At first he discussed his relations with other patients on the ward and later, with some anxiety, described early homosexual experiences. Although he once left the hospital for a three-day weekend with only 400 mg. of demerol, he usually demanded a great deal more. About a month after the beginning of anaclitic treatment he was taking 800 mg. of demerol daily. He began having ideas of oral incorporation with many references to "swallowing people." He thought he was pregnant. Having "eaten the doctor," he was carrying him as a fetus in his abdomen. He showed unusual bodily preoccupation. He drew bizarre pictures of himself with a big mouth, a long tube-like body, and male and female genitals.

When auditory hallucinations became more and more threatening, he demanded alcohol to quench "the fires" that devoured him. While he was drinking all he wanted, he was under constant supervision on the closed ward. He ate the foods which he had requested voraciously. At this time his behavior was that of a deteriorated schizophrenic patient: little contact with reality, suicidal and homocidal tendencies, auditory and visual hallucinations, and smearing of feces. His demand for alcohol and demerol stopped for one week. At all times he recognized his therapist, shook hands with him, and asked him for help. The patient described himself as being in a pit "full of fires." He talked incessantly about "lights, blue bubbles, and green water." He said he wanted to go back to his mother's stomach. He made frequent suicidal gestures in order to "get away from the voices."

On one occasion, when he had asked to see his therapist during the night, he requested milk. After it was given to him in a bottle, he began behaving like an infant. He wore diapers, spoke baby talk and often asked for his mother and father. Three or four times a day, when the therapist was dressing the patient's area of sepsis, he offered milk to the patient. The patient did not ask for alcohol again for three months. "Liquor is poison, and milk is life," he said. Although he increased his demands for demerol, his behavior improved.

A medical complication soon developed. Because of his chronically infected inguinal nodes massive edema developed in his lower extremities and on his penis. Cultures showed a great number of bacteria, most of them resistant to all antibiotics except chloromycetin. Treatment with this drug was begun immediately.

Feeling that his body was rotting away, the patient became acutely depressed. He wanted to die. His schizophrenic-like symptoms, however, disappeared. He began demanding barbiturates and lying in a semi-stuporous state day and night. Making contact with him became practically impossible. He began doubting his therapist's ability to treat him successfully and remained oblivious to the outside world. But chloromycetin treatment slowly brought the sepsis under control. The edema subsided and finally disappeared. The patient was amazed at the "miracle."

At this time, about four months after the beginning of the treatment, restrictions were placed on the patient. He was told that his period of satisfaction was over and that, henceforth, all his desires would not be fulfilled. Demerol and barbiturates were withdrawn slowly so that after three weeks the patient was off these medications. His requests for alcohol was firmly denied. His exotic foods, too, were restricted slowly so that by two months he was on the house diet. He gave up all his extra privileges on the ward. Throughout, his spirits remained good. His passivity and dependence decreased. He had no hallucinations or delusions.

The therapist began discussing discharge with the patient and helping him make plans for a life outside the hospital. A social worker suggested possibilities for jobs and housing. Progressively the patient became more self-confident. Working long hours in occupational therapy, he invented a more efficient ileostomy bag.

Now, one year after his admission to the hospital, he is talking about the "miracle" of his treatment. He refers to his therapist as a "superhuman" being who has given him a "new life."

DISCUSSION

DR. COBB: One has to be a little skeptical of his statements because he has had a lot of psychotherapy and knows what he ought to say. It is an extraordinarily illuminating case, but what intrigues me first is what relation this observation has to our understanding of the diseases we call schizophrenia, manic-depressive insanity and psychopathic reaction. Here we have symptoms of first one then another, in a man who did not show any schizophrenic reactions earlier. The other point is how much have we learned from him about anaclitic therapy?

DR. LUDWIG: This patient presented an extremely complicated problem from every point of view. His early life was disturbed, he progressively lost his father, a good grandmother and at times had severe difficulty with his mother and later with his stepfather. The death of his stepfather appeared to be important in association with the onset of his illness. He had had some difficulty at the time of his father's death, but we have not been able to recover much material about this. In so far as we know, his mother was a rejecting and hostile person. Even though we have no other evidence, during his stay here at the hospital she never came to see him.

MRS. STEELE: I saw her. We talked about what arrangements could be made for him when he got home. Neither mother nor sister was too worried about his coming home. I was not impressed by her one way or the other. She had very little to say. She accepted the fact that he had been sick. She was neutral. The sister seemed quite warm.

DR. LUDWIG: As in other cases with psychosomatic disorders in my experience, this man had a great deal of difficulty in early life. Undoubtedly he had developed a fixation in the early oral phase of his development. He seemed to do relatively well until he was thirty-one years of age. It may be that individuals who later develop psychosomatic disorders remain healthy as long as they have a security system which works for them. This security system may break down, perhaps through the death of or rejection by some close relative or perhaps even by losing a job. Such an event is a frequent precursor in many of these disorders. I have been intrigued in other cases with the curious relationship between psychosis and ulcerative colitis. It would seem likely to expect the development of addiction in individuals with very early oral fixation.

I believe it is impossible to give any clear account of just what this therapy meant to the patient. It is doubtful if we can find out from him. The first point to be made, however, is that this man was subjected for four years to extensive psychotherapy, which apparently did little to relieve his symptoms. We would like very much to know what could have been accomplished if it had been possible to use anaclitic therapy before tissue damage had occurred in his colon. At the present time, this man has lost his colon, has had his rectum removed and has had many severe secondary reactions.

It is important not to minimize the great difficulty in carrying out this type of therapy. It imposes a tremendous burden on the doctors and an even greater one on the nurses and ward personnel. I believe that our giving large amounts of alcohol and drugs up to the limit of his own desire for as long a period as we did may be open to criticism. As Dr. Sifneos has said, we finally found ourselves in a position where we were aiding his own destructive drive if we continued any longer. From what we now know about the dynamics which operate in such severely regressed patients, we might have been wiser to have fed him milk which is probably what he really wanted, rather than alcohol or drugs. In retrospect we might also have been wiser if we had stopped the alcohol and drugs and taken control before we did. However, we do not know whether or not this period of complete satisfaction of all of his desires might have been necessary to this patient in order to help him accept a dependent relationship on another person. When such a person takes drugs or alcohol, he transfers his dependence on to something else which he himself can control. Finally, he gave that control to his therapist.

It must be said that we can have no way of knowing how successful this whole procedure has been until this man has been exposed to the normal strains of life which we know will be numerous for him. If we continue to make the support available to him, he may be able to manage very well. With these patients it is often amazing how very simple things done in the course of therapy—in terms of giving support—may have a striking effect.

FOLLOW-UP

Two weeks after the staff conference, in October, 1952, the patient was discharged. He lived with his mother and sister, but he came biweekly for interviews with his therapist. Anxious and tense at first, he explained that he felt "lost." Twice he got drunk "trying to forget." Soon, however, he said he realized that what had happened was "something big." He felt he would be letting his doctor down if he did not succeed in the outside world as he had in the hospital. Slowly he began to feel self-confident. His visits to the outpatient department became more infrequent. Two months after discharge he announced that he felt

secure. "I want to stand on my own two feet." He had not been drinking. He had had several part-time jobs and was looking for full-time work. His family, he said, was "amazed" at his change.

Five months after discharge his "follow-up" was officially terminated. He understood, however, that both his therapist and his social worker would be available whenever he needed them. He was jubilant.

In the one month since he has called to report that he is in excellent spirits, is continuing to work part-time and is enjoying excellent health.

COMMENT

In addition to ulcerative colitis this patient had symptoms indicating character neurosis, depression, alcoholism, drug addiction and schizophrenia. The remissions and exacerbations of his psychosomatic illness were closely associated with the remissions and exacerbations of his psychotic behavior. When his colon was removed surgically, the patient began alternating schizophrenic behavior with severe depression. With these complicated interrelations the diagnosis was difficult. *Schizo-affective psychotic reaction with acute and chronic ulcerative colitis* was chosen as the most fitting diagnosis.

That anaclitic treatment is responsible for this patient's improvement is questionable. A remission may account for the amelioration of his symptoms. The withdrawal of drugs may have triggered his recovery. The chloromycetic treatment, by removing his infection, certainly helped eliminate his depression. On the other hand; the anaclitic treatment did give the therapist an opportunity to establish a strong, positive relationship with a severely disturbed, hostile patient. Lasting throughout his hospitalization and six months of discharge, it was the motivation for the patient's social rehabilitation.

Should such a treatment be used with other patients? The contraindications are formidable: it is costly in money; it puts a great strain on the nurses; and it often elicits unfortunate reactions from other patients. The demands on the therapist, moreover, particularly emotionally, are enormous. Unless he has positive feelings for the patient, the therapist cannot form an anaclitic relationship with him.

In an appropriate setting, however, and with a severely disturbed patient who has not responded to other forms of therapy, anaclitic treatment may be life-saving.

Clinico-pathologic Conference

Progressive Central Nervous System Disease

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. V. (No. 214631), was a white housewife, seventy-five years of age, who was admitted to the Barnes Hospital for the first time on October 2, 1952, because of anorexia and weakness. The family history was irrelevant. The past history was of interest only in that ten years before admission the patient had had symptoms suggestive of renal calculus. Under conservative treatment the symptoms disappeared and did not recur. The patient remained in good health until two months before entry when she noted the onset of progressive anorexia and weakness. Her relatives stated that three weeks before entry the patient became confused and lethargic and exhibited poorly coordinated movements. Ten days prior to admission she became dizzy and fainted. Three days before entry she vomited once, and then developed diarrhea. During the course of the two months' illness she lost 15 pounds.

At the time of entry physical examination revealed the patient's temperature to be 37.8°C., pulse 72, respirations 14 and blood pressure 150/70. She was an elderly, obese, lethargic white female who was somewhat confused but able to cooperate during the examination. The skin was warm and dry and of normal turgor. There was no significant lymph node enlargement. The pupils were round, regular and equal and reacted to light and accommodation. Because of bilateral lenticular opacities the fundi could not be visualized. The upper respiratory tract appeared normal. The lungs were clear to percussion, but scattered large rales were heard at the bases posteriorly on auscultation. The cardiac examination was within normal limits as were the abdominal and pelvic examinations. The arterial pulses in the lower legs were not palpable. There was no edema. Neurologic examination was entirely within normal limits except for the obtundity.

The laboratory data were as follows: red cells, 4,300,000; hemoglobin, 14 gm; white cells, 10,250; differential count, 66 per cent segmented forms, 21 per cent lymphocytes, 12 per cent monocytes and 1 per cent eosinophils. Urinalysis: specific gravity, 1.023; albumin, negative; sugar, negative; centrifuged sediment, 8 to 10 white blood cells and an occasional red blood cell per high-power field. Stool: guaiac negative. Blood cardiolipin test: negative. Blood chemistry: non-protein nitrogen, 17 mg. per cent; fasting blood sugar, 87 mg. per cent; 10:30 A.M. blood sugar, 121 mg. per cent; total protein, 7.4 mg. per cent; albumin, 4.0 gm. per cent; globulin, 3.4 gm. per cent; cholesterol, 178 mg. per cent; sodium, 130 mEq./L; potassium, 5.4 mEq./L. Roentgenogram of the chest revealed clear lung fields, some calcification in the aortic knob, a normal cardiac silhouette and minimal hypertrophic arthritis of the dorsal spine. Electrocardiogram was within normal limits.

The patient continued to be lethargic after admission and refused both liquid and solid foods, necessitating the administration of parenteral fluids. Because of the presence of rales at the lung bases penicillin was given. Despite this treatment, however, she became febrile on the third hospital day, her temperature rising to 38°C. The physical findings were unchanged from those recorded on admission and the white blood cell count was 7,200. Urine culture revealed coliform organisms and the patient was given mandelic acid. Although her temperature fell to normal on the seventh hospital day, she became progressively more confused and drowsy. A lumbar puncture was performed and clear fluid was obtained; the initial and final pressures were 100 and 0 mm. of water, respectively. The spinal fluid protein was 134 mg. per cent, sugar 67 mg. per cent, colloidal gold curve negative

and Wassermann test negative. There were no cells and cultures were sterile.

During the patient's second hospital week her temperature remained normal and her condition was unchanged. Blood chemical determinations on the eleventh hospital day included a serum sodium of 129 mEq./L. Other laboratory data on that day were: red blood cell count, 5,000,000; hemoglobin, 14.8 gm; white blood cell count, 14,250, differential count: 2 per cent stab forms, 83 per cent segmented forms, 14 per cent lymphocytes and 1 per cent monocytes. On the twelfth hospital day the patient complained of severe headache and had some nausea and vomiting. Because of urinary incontinence a retention catheter was inserted, and tube feedings were instituted.

On the fifteenth hospital day the patient's temperature rose, and thereafter persisted between 38 and 40°c. Penicillin, streptomycin and subsequently aureomycin were given, but none of these produced any clinical improvement. Repeated stool cultures were negative for pathogens, and agglutinations against typhoid and paratyphoid antigens were negative. During the third hospital week repeated examinations of the chest revealed diminished breath sounds and a few sticky rales at the right lung base. A chest film showed diffuse fibrosis of both upper lung fields and evidence of pneumonitis of the right lower lobe. It was suspected that the pneumonitis resulted from aspiration. Sputum cultures for acid-fast organisms were negative. Findings suggestive of thrombophlebitis involving the veins of the right leg were noted, but the inflammatory changes subsided within a few days. Frequent urinalyses were performed but the findings were not significantly different from those recorded originally. The blood nonprotein nitrogen remained within normal limits. The patient, who could no longer be aroused, was seen in consultation by a urologist who did not think that the fever could be explained on the basis of urinary tract infection. Ptosis of the right eye, nuchal rigidity and positive Kernig and Babinski signs were observed, and another lumbar puncture was performed. The initial pressure was 120 mm. and the final pressure 70 mm. of water after the removal of 5 cc. of xanthrochromic fluid. The protein content of the fluid was 220 mg. per cent, and it contained 21 mononuclear cells. Cultures for both pyogenic bacteria and acid-fast organisms were negative. A neurologist, who saw the patient in consultation, learned from a relative that ten days before admission, during the episode of syncope, the patient apparently struck her head. Films of the skull were taken and revealed calcification of the internal carotid arteries. In addition, the pineal body was at the posterior limit of its normal position.

Because of the development of the neurologic signs and the progressively downhill course the patient was transferred to the Neurosurgical service. Ventriculograms were performed and were not abnormal. Exploration for subdural hematoma was negative. Cerebrospinal fluid obtained at the time of operation was only faintly xanthochromic. The patient's coma deepened. Cisternal puncture revealed xanthochromic fluid with an elevated protein content, but there was no increase in pressure. The spinal fluid sugar was consistently normal, cultures remained sterile and India ink preparations for torula were negative. Numerous blood cultures showed no growth. During the last three weeks of her life the patient's course was one of progressive deterioration. New neurologic signs included deviation of the tongue to the right, and clonus of the right arm when the deep tendon reflexes were tested. Signs of thrombophlebitis appeared in both the left arm and left leg. The blood chemistry values remained unaltered and the patient's blood pressure remained within normal limits throughout her hospital stay. She expired quietly on December 7, 1952, two months after admission.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This patient was in the hospital for two months during her terminal illness, but despite exhaustive studies by the medical service and by various consultants a definitive diagnosis was not made. Dr. Elliott, would you begin the discussion by commenting on the x-ray films?

DR. GLADDEN V. ELLIOTT: The patient had numerous roentgenographic studies while in the hospital. The examination of the chest performed shortly after admission revealed a rather striking amount of reticulation in the periphery of both lung fields, thought to be compatible with the emphysema and interstitial fibrosis which occur with advancing age. Similarly, calcification of the aortic knob, such as was present, is not unusual in elderly patients. In the protocol mention was not made of a small calcific plaque in the apex of the left lung and

of obliteration of the right cardiac angle; the relationship of these findings to the patient's illness, if any, is obscure. Presumably the cardiophrenic angle changes could have been due to the presence of fat, to a small omental hernia or perhaps to a benign pericardial cyst. Another chest examination was obtained about three weeks later. At that time the patient was much sicker and could not be positioned properly. Under strong illumination the film revealed fine nodulation throughout both lung fields. We were unable to be certain whether this nodulation represented actual miliary infiltration or whether it was an artefact which was due to the patient's failure to take a deep breath.

DR. ALEXANDER: Was the nodulation seen on the second film absent on the initial one?

DR. ELLIOTT: As I indicated, there was a certain amount of reticulation on the first film, not unlike that commonly seen in patients in their seventies. Further, when patients do not take an adequate breath, the apparent nodulation may represent inadequate aeration rather than infiltration. It is, therefore, impossible to differentiate in this case, on the basis of the available films, between the changes of age and those of pulmonary infiltration. Relatively late in her hospital course, about four weeks after her entry, the patient had a skull examination. The striking abnormalities included calcification of the internal carotid arteries, and rather distinct demineralization of the posterior clinoid processes without definite errosion. The pineal gland was thought to be at the posterior limit of its normal position. The ventriculograms, as noted in the protocol, were thought to be within normal limits. There was symmetrical filling and a slight degree of dilatation of the lateral ventricles compatible with the patient's age. The third ventricle was midline in position and normal in size. I could not identify the fourth ventricle. Again on the ventriculograms the position of the pineal was at the posterior limit of normal.

DR. ALEXANDER: Certainly the neurologic aspects of this case are prominent. You will recall that the patient became confused and lethargic about three weeks before admission and ten days before entry she fainted. After she had been in the hospital several weeks it was learned from one of her relatives that she had bumped her head during the syncopal episode When she was admitted the most striking findings were lethargy and confusion. At the end of the second week she developed a severe headache with nausea and vomiting and soon thereafter became febrile. On the first lumbar puncture clear fluid with a high protein content was obtained. Subsequent lumbar punctures revealed that the spinal fluid was xanthochromic and contained an increased number of mononuclear cells. Dr. Jones, after you saw this patient in consultation and elicited from one of her relatives the history of trauma, you suggested that she might have a subdural hematoma. Did you also consider cerebral arteriosclerosis as an explanation for the findings?

DR. ANDREW B. JONES: It was my impression that the patient's admission originally had been occasioned by the fact that she had signs of respiratory infection, and that after entering the hospital she developed neurologic changes. The possibility of subdural hematoma came to mind because of the history of the trauma, the rather acute onset of neurologic signs and the recovery of xanthochromic spinal fluid. The latter is in itself by no means diagnostic; it may be found in a great number of intracranial lesions, but in any case ventriculography seemed indicated.

In regard to the possibility of explaining the neurologic abnormalities on the basis of cerebral arteriosclerosis I was struck by the fact that the indications were that the patient had been an extremely active person whose behavior and mental acuity belied her age. The rather rapid appearance of neurologic symptoms seemed to me more in keeping with a lesion other than arteriosclerosis.

DR. ALEXANDER: The ventriculograms were normal. Dr. Schwartz, is it possible for a patient to have a space-occupying lesion in the brain without signs of increased intracranial pressure and without abnormalities demonstrable by ventriculography?

DR. HENRY G. SCHWARTZ: Yes, it is. Particularly when lesions are above the tentorium sizable tumors can be present without there being evidence of increased intracranial pressure. Contrariwise posterior fossa lesions or lesions of the fourth ventricle may interfere with spinal fluid dynamics even when quite small. Tumors at the anterior tip of the frontal lobe or at the extreme margin of the occipital pole can become large and gradually displace brain tissue without giving rise to obstruction of the ventricular system. Generally, parasagittal meningiomas or parasagittal astrocytomas can

grow to considerable size before causing evidence of increased intracranial pressure. Finally, any brain tumor, which for some reason or other remains very small over a long period of time, may not lead to signs of increased pressure or ventricle distortion. Fortunately, such cases are uncommon and do not comprise more than 5 per cent of those which we encounter. Consequently, unless the clinical vidence of localization is quite definite, it is reasonably certain that when a ventriculogram is negative that the patient does not have a tumor. It should be emphasized, however, that if there are distinct localizing signs tumor must be suspected despite a normal ventriculogram; in such cases, exploration is often indicated.

DR. ALEXANDER: I take it, then, that in this patient the chances were less than 1 in 20 that she had a tumor.

DR. SCHWARTZ: That is correct.

DR. ALEXANDER: Dr. Levy, the first lumbar puncture revealed clear fluid, the only abnormality of which was a high protein content. It was only subsequently that xanthochromia and increased mononuclear cell counts were encountered. Would you comment on this sequence of events.

DR. IRWIN LEVY: Before I do, Dr. Alexander, may I enter a dissenting opinion on the ventriculograms?

DR. ALEXANDER: Yes, you certainly may.

DR. LEVY: It was my impression that in the lateral projection with the right side up the anterior inferior portion of the left frontal horn did not fill as well as the corresponding area on the right. I thought that the same defect could be visualized in the anteroposterior projection with the face up.

DR. ALEXANDER: I take it that you did not agree with Dr. Levy's interpretation, Dr. Schwartz.

DR. SCHWARTZ: No, I did not. There was certainly some dilatation of the ventricular system but I considered that the defect, to which Dr. Levy referred, in the inferior lateral portion of the frontal horn, was due to normal variation. In the absence of any symptoms suggestive of a lesion in the left frontal lobe, I disregarded that possibility.

DR. LEVY: Dr. Jones, didn't you demonstrate abnormal deep tendon reflexes on the right?

DR. JONES: The neurologic signs varied from day to day. On some days I could elicit pathologic signs and yet on others I was unable to do so.

DR. ALEXANDER: Can we return to the original question, Dr. Levy, concerning the appearance of cells and xanthochromic fluid?

DR. LEVY: Such changes are compatible with a number of lesions including tumor, abscess or meningeal irritation due to one of several causes.

DR. ALEXANDER: In other words, the spinal fluid findings were relatively little value in making a specific diagnosis.

DR. LEVY: That is correct.

DR. ALEXANDER: Did you entertain the possibility of brain abscess, Dr. Jones?

DR. JONES: I didn't think it likely.

DR. ALEXANDER: Would anyone else support that diagnosis?

DR. LEVY: It cannot be excluded.

DR. ALEXANDER: In the chart it was noted that a few gram-positive organisms were thought to be present on several smears, but cultures were consistently negative and so were India ink preparations. Dr. Smith, does brain abscess occur in cryptococcic infection?

DR. DAVID E. SMITH: Typically cryptococcus produces a granulomatous lesion which may lead to signs indistinguishable from those of any other pyogenic abscess. The course which characterized this patient's illness would have been an unusual one for torula.

DR. ALEXANDER: Persistent fever, which did not respond to antibiotics and which was not thought to be due to urinary tract infections, was an interesting feature of this case. Dr. Schwartz, would you comment on fever of central origin, and tell us if you believe that the prolonged hyperpyrexia observed here was due to cerebral involvement?

DR. SCHWARTZ: To answer the second portion of your question first, I see no evidence that the fever arose because of central nervous system disease. As to so-called "central fever," in general, lesions around the base of the third ventricle or in the floor of the fourth ventricle are associated with high fever or with rapid swings in temperature; in either of those instances, however, there are usually other signs which may aid in the localization of the abnormality. I would look elsewhere for the cause of this patient's fever.

DR. ALEXANDER: Pulmonary infection certainly could have caused fever. On one of the later chest films, Dr. Elliott, it was thought by

the x-ray department that this patient had pneumonitis.

DR. ELLIOTT: That is correct, Dr. Alexander. The film to which you refer was interpreted as being compatible with pneumonitis in the right lower lobe. I did not read these films originally, but in reviewing them, I was more impressed by nodulation than by changes suggesting localized pneumonitis. If this patient did indeed have miliary lesions, for example, those of tuberculosis or a fungus, they could have produced the prolonged temperature elevation.

DR. ALEXANDER: Aspiration pneumonia was considered because the patient received tube feedings while comatose and conceivably could have aspirated secretions or regurgitated stomach contents. Are there other suggestions?

DR. ALBERT I. MENDELOFF: Diffuse carcinomatosis of the lungs should also be mentioned although the fact that the patient was not dyspneic militates against that diagnosis.

DR. ALEXANDER: Dr. Skilling, the patient was originally admitted on your service. Do you wish to make any comments?

DR. DAVID M. SKILLING: The patient was first admitted to the hospital with a presumptive diagnosis of pneumonia, primarily because of the pulmonary findings. She had been getting increasingly ill for a day or two before I saw her. Subsequently, it became clear that she had serious central nervous system disease; we were particularly suspicious of tumor or of a brain abscess. After the ventriculograms were interpreted as being negative, the possibility to which you have already alluded, namely, that the changes were due to cerebral arteriosclerosis *per se*, was also considered seriously. Nonetheless, in view of the rapidly progressive course, I still favor tumor or abscess over encephalomalacia secondary to vascular disease.

DR. ALEXANDER: Dr. Wood, this patient had several episodes of thrombophlebitis which involved first her leg veins and subsequently those in her arm. Do you think this complication was of special significance.

DR. W. BARRY WOOD, JR.: It is, of course, common for patients who remain in bed for a long period of time, particularly those in the older age group, to develop thrombophlebitis in the lower extremities. It is somewhat less usual, however, for the veins in the arms to be involved. Whenever patients develop multiple thrombophlebitis, all of us think of carcinoma of the body or tail of the pancreas, the tumor most commonly associated with multiple thrombophlebitis. The entity is also seen with other forms of carcinoma. In this case, the queer neurologic findings bring to mind a much younger patient of Dr. Keith Wilson's who had saggital sinus thrombosis following pregnancy. Dr. Wilson's patient had a very bizarre and variable neurologic picture. Dr. Wilson, could this patient have had a similar lesion?

DR. KEITH S. WILSON: In the patient to whom you refer, I think the findings were much more suggestive of encephalitis than those noted here. In this case the possible miliary infiltration in the lungs suggests either tuberculosis, or as Dr. Mendeloff has suggested, carcinoma with lymphangitic spread. As far as tuberculosis is concerned it is worth mentioning that in some instances, a tuberculous abscess near the meninges but not in communication with them, may produce only minimal signs of meningitis.

DR. WOOD: I think Dr. Wilson's point is a good one. Such a lesion would be compatible with the normal spinal fluid sugar values found in this case.

DR. ALEXANDER: Dr. Levy, I presume that in view of what you have said previously you believe a neoplasm in the frontal lobe to be the most likely possibility.

DR. LEVY: Yes.

DR. ALEXANDER: What diagnosis do you wish to make, Dr. Jones.

DR. JONES: I believe the patient probably had a brain tumor, although during the course of her illness I was unable to establish that diagnosis.

DR. ALEXANDER: Dr. Schwartz, what is your diagnosis?

DR. SCHWARTZ: I favor a granulomatous lesion; as has been mentioned one can explain the pulmonary findings as well in that way.

DR. ALEXANDER: Dr. O'Leary, will you add your opinion?

DR. JAMES L. O'LEARY: I favor a neoplasm, but I agree with Dr. Schwartz that a granulomatous lesion, which would also explain the pulmonary findings, is an important alternative diagnosis.

DR. ALEXANDER: In summary, then, the concensus favors either a brain tumor or a granulomatous lesion, perhaps tuberculosis, as the explanation of this patient's illness.

Clinical Diagnoses: ? Neoplasm of brain; ? tuberculous or fungus infection of the lungs and central nervous system.

FIG. 1. Photograph showing large tumor nodules in the brain.

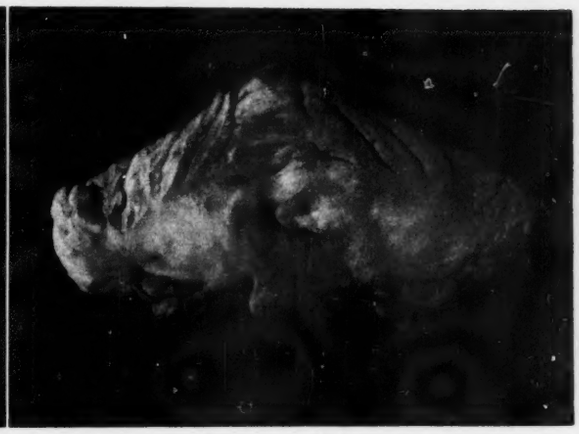

FIG. 2. Separate tumor nodule invading the fourth ventricle.

PATHOLOGIC DISCUSSION

DR. WILLIAM D. ATCHISON: The brain appeared grossly normal externally except for softening over the left parietal cortex. On section there was a very small area of old encephalomalacia of the left putamen, and a yellow granular tumor mass over the right corpus callosum. The tumor extended into the white matter over the ventricle, particularly on the right. A similar yellow granular soft tumor mass was noted in the cerebellar hemisphere on the right.

There were 120 cc. of serofibrinous fluid in the right pleural cavity, and organizing fibrinous exudate was present over the lateral surface of the lower lobes. Two bulging, fibrous, depigmented, wedge-shaped areas were seen in the right lower lobe, and there were bilateral scars and bilateral pleural adhesions at the apices. Except for the advanced generalized arteriosclerosis the other viscera were normal.

DR. DAVID E. SMITH: Dr. Atchison has described a tumor which can be recognized in Figure 1 as being predominantly in the posterior part of the brain. It apparently arose in the corpus callosum and extended largely to the right side to the occipital horn of the ventricle but it also invaded the left side. Most interestingly, there was an entirely separate nodule in the cerebellum over the fourth ventricle, somewhat to the right of center. (Fig. 2.) The principal other findings were a severe degree of arteriosclerosis involving all of the principal vessels, and wedge-shaped areas of depigmented necrotic material in the periphery of the lower lobe of the right lobe. (Fig. 3.)

Let us turn first to a microscopic section (Fig. 4) of the tumor mass as seen in the occipital lobe. The tumor is an interesting one in that the cells are quite homogeneous. The nuclei are round or kidney-shaped with prominent nucleoli; the peripheral membrane of the nucleus is prominent and the cytoplasm is relatively scanty and lumpy. I think that the diagnosis one attaches to this tumor is indicative of an attitude of mind on the part of the pathologist. This section was shown to three or four well known pathologists, all of whom said they would term it a reticulum cell sarcoma if it weren't in the brain. I have had the temerity to suggest that it is indeed a reticulum cell sarcoma despite its site of origin. About twenty-five years ago when Bailey and Cushing wrote their classic treatise on gliomas, they firmly established the fact that the majority of brain tumors arise from glial tissues and that the old diagnoses of glial sarcomas, etc., were often incorrect. There has been more recently, particularly in the last ten years or so, a reëmphasis of the importance of the small minority of tumors which actually are not glial in origin, but which are nonetheless primary in the central nervous system. In the present case, after careful gross and microscopic examination, no tumor could be demonstrated anywhere except in the two sites in the central nervous system which have been shown. The next section (Fig. 5) shows an interesting characteristic of the tumor, namely, its prominent perivascular location. Figure 6 is from a section stained to demonstrate reticulum; the fact that none was formed by the tumor is apparent. These observations emphasize the fact that there is confusion in the use of the term "reticulum cell." It will be recalled that

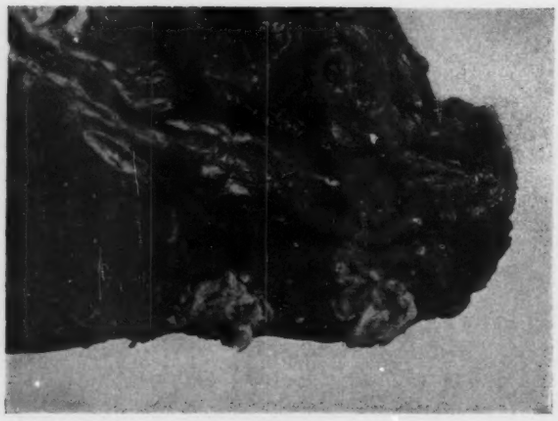

FIG. 3. Photograph of the right lower lobe of the lung; note the two wedge-shaped infarcts in the lower portion.

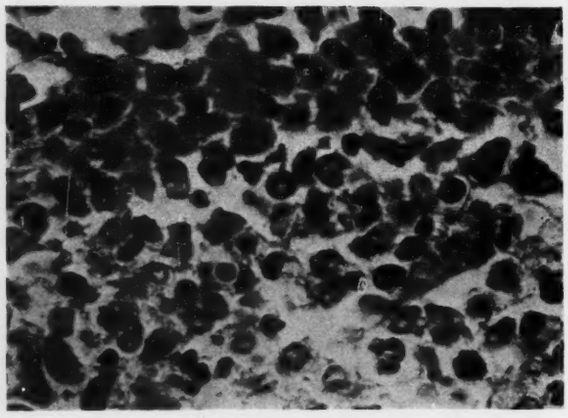

FIG. 4. Microscopic section of the tumor mass in the occipital lobe. The cells are homogeneous.

normally in lymph nodes the reticulum cells form the framework in which lymphocytes are held in position. These cells do not usually produce reticulum which is more frequently a product of fibroblasts. Reticulin fibers are found in the present tumor only about the blood vessels because the rest of the stroma of the brain contains no reticulin normally. Still another feature of this tumor was its tendency to infiltrate. In Figure 7 tumor cells are seen in the meninges. In some regions the infiltration was marked, producing sarcomatosis of the meninges, if you will. Although for the most part meningeal involvement was not so striking, it might have accounted for some transitory phases of the meningeal irritation.

Figure 8 is taken from a section from one of the wedge-shaped areas in the lower lobe of the right lung. There is a central, liquefied area with few inflammatory cells, and about that a zone of fibroblastic proliferation in which there is a loss of the architectural pattern—in other words, a zone of organization. Grossly and microscopically this lesion is typical of an infarct. The absence of inflammatory cells indicates that it was not an infected pulmonary infarct, but the fact that it was necrotic, with fluid in its center, plus the gross appearance suggest that it belongs in the so-called depigmented category. It is generally considered by pathologists that it takes about six weeks for a depigmented infarct of the lung to develop. Therefore, even though the infarcts were not seen on the chest films during life, it is probable that they were present during most of the hospital course at least. The junction between the center zone and the periphery of the infarct is shown under higher power in Figure 9. The absence of inflammatory cells is again noted. Additional pathologic change was also found in other sections of the right lung. Thus, in a few alveoli, the presence of an inflammatory exudate indicated that there was some bronchopneumonia terminally. (Fig. 10.) Changes compatible with purulent bronchitis were also found in a few sites. These facts, coupled with the presence of a moderate amount of serofibrinous fluid and rather extensive fibrous adhesions in the right pleural cavity, probably explain the obliteration of the cardiophrenic angle, reported by the radiologists; possibly they also were responsible, in part, for the rather confusing x-ray findings in the chest films taken late in the course.

There remain aspects of this case which are difficult to understand. In the first place, why did a tumor of this size escape detection on the ventriculograms? The studies were done about two weeks before the patient died, but I don't believe the tumor developed to the size noted at autopsy in just two weeks. In this regard, I would point out that the general weight of the brain was only 1,260 gm., despite the presence of such a large tumor mass. Further, the patient had severe arteriosclerosis of the vessels in her brain and encephalomalacia on the left side. It is possible that if a ventriculogram had been done six months prior to death, distinct evidence of atrophy of the cerebral hemispheres might have been demonstrated. It may be postulated, therefore, that the fact the brain was relatively small in relation to the cranial cavity permitted the development subsequently of a rather large tumor without leading to definite distortion of the brain and the usual signs of increased intracranial pressure.

A word or two about the diagnosis of malig-

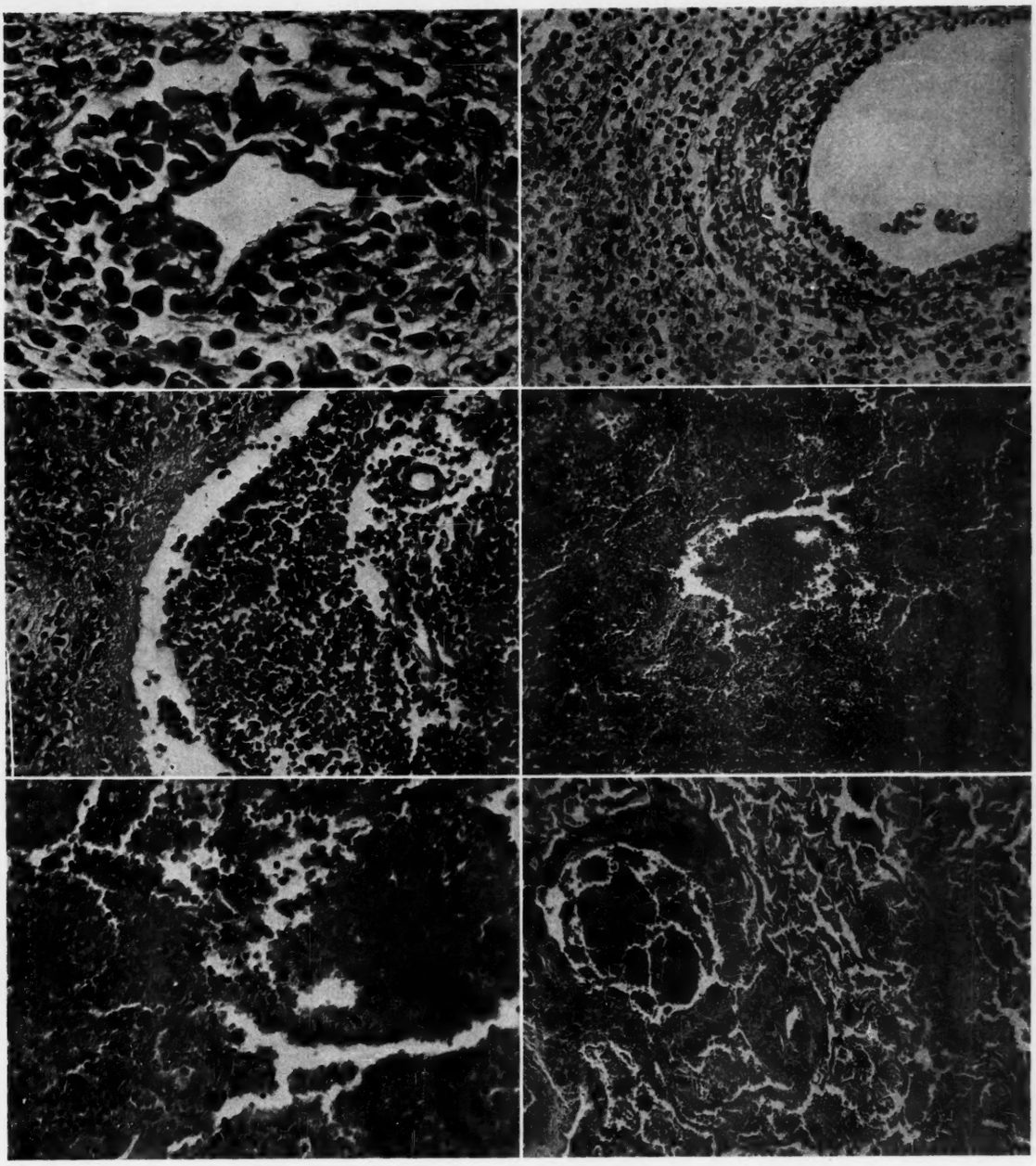

FIG. 5. Another section of the tumor showing its perivascular position.

FIG. 6. Section of the tumor stained for reticulum; none is demonstrated.

FIG. 7. Tumor cells in the meninges.

FIG. 8. Photomicrograph of one of the infarcts in the lung. The necrotic center and the fibroblastic peripheral zone are seen.

FIG. 9. The junction between the two zones of the infarct seen under high power; note the absence of inflammatory cells.

FIG. 10. Low power view of another area of the lung showing changes typical of bronchopneumonia.

nant lymphoma of the central nervous system is in order. There have been cases reported which correspond to the varied histologic patterns of the lymphomas, including primary Hodgkin's disease. Relatively few of them, however, have been subjected to complete autopsies, and it is only in the latter that one can be assured that the tumor existed only in the central nervous system. It is interesting that in the brain lymphomatous tumors tend to be situated in the midline portions; for example, many of the cases show involvement of the fornix, pillars of the fornix and structures about the hypothalamus. Most of the cases occur in the older age group. Finally, it is also pertinent that the signs and symptoms recorded in the protocols of the published cases include fever and rather bizarre clinical courses not unlike the one experienced by the patient.

DR. ALEXANDER: Are there any questions or comments?

DR. MENDELOFF: Do you think a cell block on the spinal fluid might have helped in making the correct diagnosis.

DR. SMITH: In this particular case it might well have.

DR. WOOD: Dr. Smith, from what cell in the brain did this tumor arise?

DR. SMITH: Your question is an interesting one; the answer is speculative but reasonably well founded. The microglial cells of the brain are derived from the reticuloendothelial system. Russell, in England, and others have described what I interpret as essentially the same tumor under the term "microgliomatosis." However, the microglial cells are probably not the only source of the phagocytic cells in the central nervous system which respond in tremendous numbers to various destructive lesions such as acute encephalomalacca. It is likely that a number of cells exist in a resting state in the mesodermal tissue about blood vessels. Perhaps a tumor such as this one, oriented to blood vessels as it was, arose from the latter cells. Considering the multiplicity of origin of lymphosarcomatous tumors elsewhere in the body, it is also conceivable that the tumor cells came by way of the blood stream and localized in the brain. Since in this case tumor was found only in the brain, it probably arose from a cell there.

Final Anatomic Diagnoses: Primary malignant lymphoma (reticulum cell sarcoma) in the posterior corpus callosum, adjacent right posterior parietal lobe and in the right lobe of the cerebellum; organizing depigmented infarcts in the lower lobe of the right lung; arteriosclerosis, advanced and generalized; focal old encephalomalacia in the left putamen and right parietal cortex.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Research Society Abstracts

The Southern Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE SEVENTH ANNUAL MEETING, NEW ORLEANS, LOUISIANA, JANUARY 31, 1953

EFFECTS OF CORTISONE ON FLUID AND ELECTROLYTE BALANCE IN NORMAL RABBITS. *J. K. Aikawa and Eloise L. Rhoades,** Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

Cortisone acetate in dosages of 4 and 25 mg. daily was given subcutaneously to two groups of seven normal adult male rabbits weighing 2.4 to 3.2 kg. for two and three weeks, respectively. Weekly external balance of Na and K, the exchangeable potassium content by the radioisotopic method, and serum Na and K concentrations were determined. The results were compared with the baseline values in each animal. The following statistically significant changes were found: after seven days on 4 mg. the body weight increased 0.16 kg., serum Na concentration decreased 9.9 mEq./L.; after fourteen days serum Na and K concentrations increased by 7.24 and 0.5 mEq./L., respectively. Twenty-five mg. daily produced the following changes: after seven days the animals were in negative K and Na balance, serum Na concentration was increased by 4.3 mEq./L.; after fourteen days negative Na and K balance continued, exchangeable potassium content (Ke) decreased 30.6 mEq., serum Na concentration increased 7.1 mEq./L. Body weight and Na and K balance changes persisted one week after cortisone was discontinued. All of the fluid and electrolyte changes previously described during cortisone therapy in diseased states have been produced in normal rabbits by the administration of these dosages of hormone.

EFFECTS OF DIGITOXIN ON FLUID AND ELECTROLYTE DISTRIBUTION IN NORMAL RABBITS. *J. K. Aikawa*, Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

Preliminary dose-response studies revealed that intravenous injection into normal rabbits of 0.2 mg./kg. of digitoxin consistently produced transient hypernatremia at three hours followed by hyponatremia at twenty-four hours. In order to localize changes in the internal distribution of sodium six animals were sacrificed 24 hours after injection of 0.2 mg./kg. Tissue analyses were performed by the radiosodium method; tissues from normal animals were used as controls. The following significant reductions in radiosodium spaces were found: lung, 24.77 $\pm$ 2.15 per cent (s.e.), control, 37.10 $\pm$ 1.35 per cent; spleen, 13.70 $\pm$ 1.05 per cent, control, 19.79 $\pm$ 1.05 per cent; adrenal, 11.55 $\pm$ 0.98 per cent, control, 14.98 $\pm$ 0.44 per cent; skeletal muscle, 6.52 $\pm$ 0.43 per cent, control, 10.07 $\pm$ 0.58 per cent. No significant difference in total radiosodium space was found.

Effects of daily administration of 0.1 mg./kg. of digitoxin for seven days on potassium and sodium balance were determined in seven male animals. When compared with baseline values, body weight increased after seven days; the exchangeable potassium content (Ke), as measured by the K^{42} method, was reduced by 35 mEq. and the serum K concentration was decreased by 0.4 mEq./L. Seven days after discontinuation of digitoxin urinary excretion of sodium was increased and that of potassium was decreased. Serum Na concentration was increased by 2.3 mEq./L.

STUDY OF RADIOACTIVE PHOSPHORUS ACTIVITIES IN PLEURAL EFFUSIONS. *Robert E. Bauer, Irwin H. Moss and Aubrey B. Richardson (introduced by Theodore E. Woodward)*, Department of Medicine, University of Maryland, School of Medicine, Baltimore, Md.

Our preliminary studies are concerned with the measurement of P^{32} activities in pleural effusions obtained from twenty-six patients who had received tracer dosages of radioactive phosphorus. In each case an attempt was made to correlate P^{32} activity with a proven etiologic diagnosis, as well as the erythrocyte count, leukocyte count and total protein contained in the effusion fluid. P^{32} in doses of 200 μc. were

* Asterisk indicates invited authors; not members of the Society.

administered orally or intravenously. After twenty-four hours samples of blood and pleural fluid were withdrawn and centrifuged. The "beta activities" in accurately measured aliquots of plasma and cell-free pleural fluid were determined and expressed as an equation:

$$\text{Index} = \frac{\text{cell free fluid (counts/min./cc.)}}{\text{plasma (counts/min./cc.)}}$$

Eight patients with chronic non-malignant disease showed an index ranging from 0.20 to 0.42 (average 0.34). Five patients with acute inflammatory disease showed an index ranging from 0.49 to 0.63 (average 0.56). Twelve patients with malignant disease showed an index ranging from 0.42 to 1.50 (average 0.77). One patient with malignant disease who had received deep x-ray therapy showed an index of 0.28. Additional data indicate that there is no correlation of the index with the number of erythrocytes, leukocytes, or the amount of protein.

These preliminary results reveal that there are noteworthy differences in P^{32} activities of pleural effusions occurring in the aforementioned groups, and that the index is dependent upon factors other than the number of erythrocytes or leukocytes, or the amount of protein present. If additional studies support current data, it is suggested that in properly selected cases this test may be of distinct diagnostic value in differentiating benign and malignant pleural effusions.

METABOLIC STUDIES ON THE HUMAN HEART *in vivo*. *R. J. Bing, M. Taeschler,* A. Siegel,* A. Vitale* and F. Balboni,** Departments of Medicine and Physiology, Medical College of Alabama, Birmingham, Ala.

The glucose, pyruvate and lactate metabolism of the human heart *in vivo* was studied in thirty patients. In some of these cardiac disease was absent; others had low output failure or hyperkinetic heart disease. Coronary vein blood was obtained by coronary sinus catheterization and coronary blood flow was determined with the nitrous oxide method. In some instances the extraction and utilization of carbohydrates were studied during glucose infusions resulting in rising glucose blood levels.

Maximal glucose, pyruvate and lactate utilizations were observed only after arterial glucose levels of at least 100 mg. per cent had been obtained. Below these concentrations the glucose, pyruvate and lactate oxygen extraction ratios (the percentage of oxygen used in the aerobic combustion of glucose, and the like) were low, indicating that under those conditions the heart used substances other than carbohydrates. The human heart consumed relatively more glucose than lactate. In patients with low output failure the maximal glucose, pyruvate and lactate extractions and their oxygen extraction ratios were increased. As the cardiac work was diminished the conversion of energy derived from carbohydrates into mechanical work was defective. In patients with hyperkinetic hearts myocardial carbohydrate extractions and their oxygen extraction ratios were diminished.

EFFECT OF TUBERCULOUS INFECTION ON SUCCINIC DEHYDROGENASE ACTIVITY IN GUINEA PIG TISSUE. *S. N. Chaudhuri, Samuel P. Martin and Philip Khairallah (introduced by Eugene A. Stead, Jr.)*, Department of Medicine, Duke University School of Medicine, Durham, N. C.

As part of a study to relate cell metabolism and manifestations of infection the effect of tuberculous infection and tuberculin shock on intracellular enzymes was studied. The experimental animals were guinea pigs. Succinic dehydrogenase was measured by the use of tetrazolium.

There is a diminution of succinic dehydrogenase activity in the kidney of animals infected with H37Rv, in all organs of animals infected with BCG, and in all organs of sensitized animals shocked with tuberculin. The absence of lowered activity in other organs of the H37Rv infected group was attributed to inflammatory cells. The depression of succinic dehydrogenase of infected and shocked tissue could be restored to normal by addition of a dialysate of normal guinea pig tissue or beef kidney. The material in the dialysate was purified by chromatography and found to have an ultraviolet absorption maximum at 260 mμ, gave a positive ninhydrin reaction, and had an Rf value of 0.65 in tetrahydrofurfuryl alcohol.

These data would indicate that there is a loss of a material necessary for optimal succinic dehydrogenase activity in infected and shocked tissue. The role of this material in the pathogenesis of the lesion and in the manifestations of the disease is under study.

DYNAMICS OF AURICULAR CONTRACTION AND G-H UPSTROKE IN THE BALLISTOCARDIOGRAM. *Lynn Christianson* (*introduced by T. R. Harrison*), Department of Internal Medicine, Medical College of Alabama, Birmingham, Ala.

Simultaneously recorded ballistocardiograms, electrokymograms, electrocardiograms, jugular pulses and heart sounds were used to correlate ballistic forces with physiologic events.

Auricular contraction: Normal ballistocardiograms usually have one predominant footward movement but may have a headward-footward or one headward movement. Isolated auricular complexes observed in complete heart block show the auricular ballistocardiographic pattern of a small footward movement followed by a larger headward-footward movement and terminated by a small headward movement.

These varying movements may be the result of arrest of blood flow in the superior and inferior venae cavae due to rising auricular pressure at onset of auricular contraction. The footward movement which predominates in most normal ballistocardiograms is perhaps due to expulsion of blood from auricles into ventricles as auricular contraction procedes. The length of time between onset of auricular and ventricular contractions has a direct effect on the number of auricular deflections seen, as the terminal auricular forces are probably often summated with or masked by the onset of ventricular contraction.

G-H upstroke: The G-H upstroke on normal ballistocardiograms shows the following time relationships: (1) it begins simultaneously with or 0.02 to 0.04 seconds before first heart sound; (2) it may begin simultaneously with or as much as 0.04 to 0.08 seconds after QRS, but never begins before QRS. Ballistocardiograms made in patients with auricular fibrillation frequently show G-H upstroke although the auricles are not contracting at all. Ballistocardiograms made in patients with complete heart block show an occasional isolated ventricular complex with G-H upstroke.

From these data we conclude that the G-H upstroke must be related at least partially to ventricular activity and cannot be due wholly to auricular activity, although it may frequently be a summation of the two forces.

ERYTHROLEUKEMIA. *Evelyn V. Coonrad* and R. W. Rundles*, Department of Medicine, Duke University School of Medicine, Durham, N. C.

Erythroleukemia is a variant of myelogenous leukemia in which the red cell precursors are predominantly affected. The hematologic features of the disease and the response to therapy have been studied in eight patients. Anemia was the presenting finding in all instances. The duration of the illness ranged from eleven months to over five years. Leukopenia, some immaturity of the circulating granulocytes, and thrombocytopenia were present in four patients. Two had positive serologic tests for syphilis apparently not indicative of luetic infection. The bone marrow in five showed a disparity in nuclear cytoplasmic maturation that could not be distinguished with certainty from the megaloblastic changes that result from nutritional deficiency. The fecal urobilinogen excretion determined in two patients was moderately increased.

None of the group responded to liver extract, vitamin B_{12} or folic acid therapy. Three were given citrovorum factor, with ascorbic acid in one instance, without response. One patient treated with urethane in sufficient dose to produce leukopenia required fewer blood transfusions. His disease ultimately became more typical of granulocytic leukemia and terminated fatally. Splenectomy was performed in two patients but was of no benefit. Two patients were treated with ACTH and cortisone; one was considerably benefited.

PHOSPHOLIPID AND NUCLEOPROTEIN METABOLISM IN RABBITS INOCULATED WITH PAPILLOMA (SHOPE) VIRUS. *W. E. Cornatzer, Duane G. Gallo,* John P. Davison* and R. G. Fischer,** Departments of Biochemistry and Bacteriology, University of North Dakota Medical School, Grand Forks, N. D.

Thirty domestic rabbits were inoculated with papilloma (Shope) virus and maintained on stock diets. Three to five months after inoculation with the virus both the control and experimental animals were injected with a solution of phosphate containing radioactive phosphorus. They were sacrificed after ten hours and radioactivity and total phosphorus determinations were made on the inorganic, phospholipid and nucleoprotein phosphorus fractions from the papilloma, skin, liver, spleen, heart, kidney and muscle. The relative specific activities of the phospholipid and nucleoprotein indicated significantly increased synthesis of these fractions in the papilloma as compared to normal skin.

The rates of synthesis of the nucleoprotein and phospholipid phosphorus in the liver, muscle, kidney, spleen and heart of the animals inoculated with the virus showed no significant difference from the controls.

Cortisone administered intramuscularly (7.5 mg./day) for one to five months caused very little change in the synthesis of the nucleoprotein and phospholipids in the various tissues except for a slight reduction in the rate of turnover of these fractions in the papilloma.

EFFECT OF HIGH AND LOW PROTEIN ON N^{15} EXCRETION RATES FOLLOWING INJECTION AND INGESTION OF TAGGED GLYCINE IN NORMAL SUBJECTS. *K. R. Crispell,* William Parson and Gardner Harden,** Department of Medicine, University of Virginia, Charlottesville, Va.

Three normal subjects in nitrogen equilibrium on a diet containing approximately 1 gm. protein/kg. body weight excreted in the urine in twenty-four hours approximately 17 per cent of N^{15} given as glycine intravenously. Increase of dietary protein to approximately 2.5 gm./kg. body weight increased the excretion of N^{15} in the urine in twenty-four hours to 31 per cent; and lowering of the dietary protein to 0.25 gm./kg. body weight decreased the excretion of N^{15} in the urine to 4.3 per cent. It would appear that the amount of protein in the diet alters the handling of amino acids given intravenously.

The excretion rates of N^{15} following the intravenous injection of N^{15} glycine have been compared with the rates following ingestion of N^{15} glycine with the breakfast meal. The excretion rate of N^{15} in the urine in twenty-four hours following the ingestion of N^{15} glycine while on a diet containing 1 gm./kg. body weight was 27 per cent as compared to 17 per cent when given intravenously. However, when the protein content of the diet is changed the same pattern of excretion is observed.

FUNGISTATIC AND TUBERCULOSTATIC ACTIVITY OF ALKYL AMINES. *Martin M. Cummings, Paul C. Hudgins,* Ernest H. Runyon* and Morris Tager,** Tuberculosis Research Laboratory, Veterans Administration Hospital, Atlanta, Georgia, and Departments of Medicine and Bacteriology, Emory University School of Medicine, Atlanta, Ga.

A series of fifteen alkyl amines, varying in carbon chain length from C_{10} to C_{15}, were tested against pathogenic strains of Mycobacterium tuberculosis, Coccidioides immitis, Blastomyces dermatitidis, Candida albicans, Nocardia asteroides, Cryptococcus neoformans, Sporotrichum schenckii and Histoplasma capsulatum. Representative of the compounds tested, 2-aminotridecane inhibited the growth of tubercle bacilli and pathogenic fungi at a range of 1 to 10 μg./ml. In general the most active fungistatic compounds were mono-amines such as 1-methylamino dodecane whereas the tuberculostatic agents included diamines like 1-11 diamino undecane. The relationship of chemical structure to antimicrobial activity suggests that the mechanism of action might be related to mono- and diamine oxidase enzyme systems of the micro-organisms.

In vivo study of selected compounds indicated some antimicrobial potential but disclosed sufficient toxicity to preclude clinical use in their present state.

THE KINETOCARDIOGRAM (PRECORDIAL MOVEMENTS). *E. E. Eddleman, Jr. (introduced by T. R. Harrison)*, Department of Internal Medicine, Medical College of Alabama, Birmingham, Ala.

A simple method has been devised to record precordial movements with the use of a bellows pick-up. Motions from an amplitude of 1 μ to 100 μ may be recorded with frequencies up to 50 vibrations/sec. Records were obtained over the anterior chest wall in positions corresponding to V_1 through V_6 of the conventional precordial electrocardiographic nomenclature and designated as KV_1, etc., to differentiate the two. Heart sounds, carotid pulses and displacement ballistocardiograms were recorded simultaneously.

A characteristic pattern has been noted in normal individuals. A marked similarity between comparable positions occurs but records differ widely over the various positions of the chest wall. Over the right ventricular area outward movements occur before the first heart sound. There is an inward movement associated with ejection systole followed by a slow outward movement which in general parallels the I-J-K wave of the ballistocardiograph. Records in the region of the apex have a sharp outward movement in isometric contraction which is most pronounced in subjects with a forceful impulse. An inward, followed by an outward, movement may be noted during isometric diastole while

rapid filling may be associated with an inward motion contrary to what would be expected.

One possible explanation of the various waves recorded would assume separate contraction and relaxation of each of the four main ventricular muscle bands and their effect on the position, shape and volume of the heart.

INFLUENCE OF ACTH, ADRENAL STEROIDS AND COLD STRESS ON FASTING KETOSIS IN THE RAT. *Frank L. Engel, James L. Scott, Jr.* and Mildred G. Engel,** Department of Medicine, Duke University School of Medicine, Durham, N. C.

Ketosis is a well known response to fasting and is accentuated by certain stressful stimuli, notably cold exposure. The adrenal cortex has been implicated in this response since ketosis is reported not to occur readily in the absence of the adrenals and ACTH has been reported to increase blood ketone levels in normal animals. Our data indicate that adrenal steroids inhibit rather than stimulate ketosis. The data may be summarized as follows: (1) Blood ketone levels are significantly lower than normal during a ten-day fast in cortisone or hydrocortisone treated rats. (2) The hyperketonemia of cold stress during a five-day fast is abolished by adrenal steroid treatment. (3) Rats acclimated to cold by exposure to 4°C. for one month develop marked adrenal hypertrophy and do not exhibit ketosis during a subsequent fast. (4) ACTH and growth hormone cause a prompt increase (3.5 hours) in blood ketone levels in normal as well as cortisone-maintained adrenalectomized rats, suggesting that the ketonemia reported by others represents an extra-adrenal effect of ACTH, probably due to its contamination by a ketogenic factor from the anterior pituitary. (5) ACTH and growth hormone do not cause ketosis in the DOCA or salt-maintained adrenalectomized rat, suggesting that the adrenal cortex may be necessary but not responsible for ketosis.

CEREBRAL HEMODYNAMICS AND METABOLISM OF DIABETIC SUBJECTS. *Joseph F. Fazekas, Alice N. Bessman and Nicholas J. Cotsonas, Jr.* (*introduced by Hugh H. Hussey*), Department of Medicine, Gallinger Municipal Hospital, Washington, D. C.

Cerebral blood flow, vascular resistance and metabolism were studied in young (sixteen to forty-three years of age) and elderly (fifty-four to seventy-three years of age) diabetic subjects and were compared with non-diabetic subjects of similar age groups. Eight of the younger diabetic subjects were known to have had diabetes for over ten years. Despite the fact that the diabetes was not rigidly controlled and some of the patients had evidence of vascular disease in other organs, the values obtained for cerebral blood flow, vascular resistance and metabolism were not significantly different from those found in the control subjects.

EXCHANGEABLE POTASSIUM IN CIRRHOSIS OF THE LIVER. *John H. Felts, Jr.,* J. K. Aikawa and George T. Harrell*, Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest College, and the North Carolina Baptist Hospital, Winston-Salem, N. C.

Available potassium may be a limiting factor in protein synthesis, which appears to be depressed in varying degree in cirrhosis. Exchangeable potassium (Ke) was determined by radioisotope dilution in one woman and eleven men with cirrhosis; single determinations were carried out in seven instances while five individuals were studied two or more times. Eleven patients had initial values (1,360–2,663 mEq.) below the normal ranges; Ke/wt. did not increase significantly with diuresis in two males with ascites despite administration of dietary potassium supplements; Ke/wt. in two subjects without ascites increased by at least 20 per cent (38.8 to 50.8 and 26.9 to 34.9 mEq./kg.) on diet alone. Hypoalbuminemia was present in nine patients with low Ke; serum potassium was normal in six individuals with low Ke while hyperkalemia was present terminally in one ascitic subject with the "low-salt syndrome" and a low Ke. These data suggest that a deficit of exchangeable potassium occurs frequently in cirrhosis.

VERATRUM TREATMENT OF TOXEMIA OF PREGNANCY: A CONTROLLED STUDY. *Frank A. Finnerty, Jr. and George J. Fuchs* (*introduced by Hugh H. Hussey*), Department of Medicine, Georgetown University School of Medicine and Georgetown Medical Division, and Georgetown and George Washington Obstetrical Divisions, Gallinger Municipal Hospital, Washington, D. C.

In 100 cases of severe pre-eclampsia (Dieckmann's classification) alternate patients received purified extracts of Veratrum viride intramuscularly; the others received pentobarbital and magnesium sulfate intravenously.

In the veratrum group the average diastolic blood pressure decreased 23.1 mm. Hg. Complications included vomiting (nine cases) and fetal death (three cases). In the pentobarbital group the average diastolic pressure increased 4.2 mm. Hg. Complications were oliguria (two cases), coma (four cases), cerebrovascular accident (one case), fetal death (three cases).

Twelve cases of eclampsia treated with intravenous veratrum were compared with twelve cases treated with pentobarbital and magnesium sulfate. In the veratrum group the average diastolic pressure decreased 28.3 mm. Hg. Convulsions occurred in seven instances after treatment was started. Complications were vomiting (ten cases) and fetal death (two cases). In the pentobarbital group the average diastolic pressure decreased 3.3 mm. Hg. Convulsions occurred in nine cases after treatment was started. Complications were oliguria (six cases), anuria (three cases), postpartum psychosis (two cases), atelectasis (two cases), cerebrovascular accident (one case), fetal death (four cases) and maternal death (one case).

These data in comparable cases at the same institution suggest that veratrum therapy is a safer and more effective method of management of toxemia of pregnancy than the currently accepted treatment.

EFFECT OF HEAD-UP TILTED POSITION ON RENAL HEMODYNAMICS AND WATER AND ELECTROLYTE EXCRETION IN PATIENTS WITH HYPERTENSION AND RENAL DAMAGE. *Ralph V. Ford,* Lewis C. Mills* and John H. Moyer*, Departments of Medicine and Pharmacology, Baylor University College of Medicine and the Medical Research Departments of the Veterans Administration Hospital and the Jefferson Davis Hospital, Houston, Tex.

Renal function was determined by standard technics in twenty male patients with hypertension. There was associated renal damage in fourteen cases as indicated by GFR less than 95 ml./min. (inulin and creatinine clearance). Glomerular filtration rate, renal plasma flow (PAH clearance), TmPAH and the rate of water, sodium and potassium excretion were determined in the control state and after 60 degrees head-up tilting. The patients were arbitrarily divided into four equal groups on the basis of control RPF in ascending order. There was no significant difference in the response between any of these four groups of patients or in a group of patients with normal blood pressure. There was a 10 per cent drop in mean blood pressure in the tilted position but a 29 per cent drop in GFR and 28 per cent drop in RPF, indicating an increase in renal vascular resistance. There was also an 18 per cent drop in TmPAH, indicating a decreased number of functioning nephrons as well as a decrease in filtration in those nephrons remaining. The hematocrit was not significantly altered (5 per cent increase). The rates of water and sodium excretion were depressed (50 per cent and 60 per cent, respectively) more than any other process studied. Potassium excretion was depressed 25 per cent.

The data indicate that the tilted position inaugurates a series of vasoconstrictive influences at the expense of normal renal hemodynamics and also results in a decline in water and sodium excretion greater than the increase in renal vascular resistance. The data show no difference in reactivity to these vasoconstrictive influences in the kidney of a patient with hypertension as compared to normal subjects. The presence of renal damage did not alter this response.

COMPARISON OF THE HEMODYNAMIC EFFECTS OF HEXAMETHONIUM AND APRESOLINE IN MAN. *Edward D. Freis, John C. Rose,* Edward A. Partenope* and Frank A. Finnerty, Jr.,** Department of Medicine, Georgetown University School of Medicine, and the Veterans Administration Hospital, Washington, D. C.

Following hexamethonium there is a decrease in cardiac output (Fick) unless cardiac failure is present, in which case there is an increase. In patients with compensated hearts the total peripheral resistance either remains unchanged or decreases only slightly. Pressures on the right side of the circulation uniformly decrease. By contrast, following apresoline cardiac output almost doubles and the total peripheral resistance decreases markedly. The pressures on the right side of the circulation increase. Thus aside from the decrease of mean arterial pressure the changes following hexamethonium are directly opposite to those of apresoline.

The increased cardiac output following apresoline results in an increase not only of renal but also of hepatic-portal blood flow, the latter being especially marked. Apresoline effects therefore resemble the pyrogenic reaction. These hemodynamic changes are in contrast to

those of hexamethonium which produces a decrease of renal flow and negligible alterations in hepatic-portal flow.

These divergent hemodynamic effects of hexamethonium and apresoline oppose and therefore tend to neutralize each other; while at the same time both act synergistically to reduce the blood pressure. These observations provide a rational basis for the use of such combinations in the treatment of hypertensive patients.

RENAL CHANGES IN EXPERIMENTAL HYPERTENSION. *Melvin L. Goldman, Henry A. Schroeder and Gustave J. Damin,** Hypertension Division, Departments of Internal Medicine and Pathology, Washington University School of Medicine, St. Louis, Mo.

Periodic biopsies were taken during a control period and yearly for five years in approximately fifty hypertensive dogs. Three groups were observed in which hypertension was induced by: (1) moderator nerve section (neurogenic); (2) a Goldblatt renal artery clamp or a silk pouch applied to only one kidney (renal); and (3) both nerve section and clamp or silk pouch on one kidney. Biopsies were taken subsequently from the contralateral kidney. The choice of dog was important (Schroeder and Goldman. *Circulation*, 5: 730, 1952). Zenker-formal fixative was used and Heidenhain azocarmine-aniline blue, periodic acid leukofuchsin, and hematoxylin and eosin stains were performed on all biopsy specimens.

The following morphologic changes were noted in all groups of dogs in order of decreasing frequency: (1) thickening of the basement membrane of the glomerular capsule; (2) thickening of the basement membrane in the glomerular tuft, and (3) an increase in intercapillary substance. No significant changes in the arterioles and no alteration in the juxtaglomerular complex or the tubular basement membrane was observed. Hypertension appeared responsible for the alterations; pyelonephritic areas were not considered. Changes began after six to twelve months and progressed slowly.

Preliminary observations on renal biopsies from human subjects with arterial hypertension not related to primary renal diseases were taken at the time of sympathectomy. In all cases there was arteriolar sclerosis and thickening of the capsular basement membrane, and a slight to moderate increase in intercapillary substance. No changes were observed in the basement membrane of the glomerular tuft. Whether or not the sequence of morphologic change is the same in the hypertensive human being as in the hypertensive dog will require further investigation.

EFFECT OF ACUTE HEMORRHAGE ON HEPATIC BLOOD FLOW AND SPLANCHNIC OXYGEN CONSUMPTION OF THE DOG. *L. W. Hamrick, Jr.** *and J. D. Myers*, Department of Medicine, Duke University School of Medicine, Durham, N. C.

Attention has been focused on reduced blood flow and deficient oxygen supply to the liver as being important in determining the irreversibility of hemorrhagic shock and in producing many of the metabolic alterations in all types of shock. Therefore the changes in hepatic blood flow (HBF) and splanchnic oxygen consumption (SpO_2) were determined by the BSP extraction method in a series of dogs under chloralose anesthesia before and following a single acute hemorrhage of approximately 34 to 63 per cent (average 48 per cent) of the blood volume. This type of hemorrhage was chosen because of its resemblance to acute hemorrhagic shock in man. Thirty to sixty minutes following rapid arterial hemorrhage there was a consistent and highly significant reduction in HBF, usually greater than 50 per cent. Despite this there was no significant change in SpO_2 even with a 75 per cent decrease in HBF. The reduction in HBF occurred at times in the absence of significant hypotension and was reversible by reinfusion.

It is concluded that acute reduction of circulating blood volume produces a striking diminution in HBF but does not alter oxygen consumption of the splanchnic area, and presumably the liver, due to the remarkable power of this area to increase the A-V oxygen difference.

IMPORTANCE OF OXYGEN IN REGULATING BREATHING DURING TISSUE HYPOXIA. *J. B. Hickam*, Department of Medicine, Duke University School of Medicine, Durham, N. C.

Blood oxygen tension is usually considered relatively unimportant in regulating ventilation. This view derives from measurements made at rest in which large falls in arterial oxygen tension evoke only moderate ventilation increases.

The influence of oxygen in regulating breathing has been studied by substituting oxygen for air in various experimental situations; the resultant drop in ventilation volume is a measure

of the pre-existing stimulus or "tone." Arterial blood gas values were followed. By this means it was found that a significant part of the ventilation volume during exhausting exercise is supported by this "oxygen tone," although arterial oxygen remains within normal limits. Similarly, persons with severe congestive failure (orthopneic) have much more of their ventilation (thirty-seven per cent in eight subjects) supported by this "tone" than would be expected in normal subjects with the same arterial oxygen tension. The hyperpnea following release of occluding arterial tourniquets is markedly dependent upon "oxygen tone." Preliminary results suggest that this also applies to the hyperpnea following re-expansion of plasma volume in dogs which have been in hemorrhagic shock.

These results suggest the generalization that blood oxygen tension becomes very significant in regulating breathing when tissues with a large oxygen debt are open to the circulation.

FURTHER OBSERVATIONS WITH THE USE OF TOLUIDINE BLUE IN BLEEDING STATES. *J. E. Holoubek, W. J. Hollis, Edwin F. Chanton and Richard B. Langford* (*introduced by Robert H. Bayley*), Shreveport, La.

A heparin-like material has been found in the blood in certain cases of thrombocytopenia with bleeding. The basic dye toluidine blue has been used to inactivate this material and stop the bleeding.

Toluidine blue and/or protamine sulfate titrations were used for determination of the amount of the heparin-like material in the blood stream. Seventy-two patients were studied; thirty-five were used as normal controls. Thirty-seven patients had abnormal bleeding tendencies with or without thrombocytopenia. Of these sixteen showed the presence of a large amount of heparin-like material in the blood streams and all of these patients had thrombocytopenia, nine had leukemia, two toxic thrombocytopenia, two aplastic anemia, one acute miliary tuberculosis of the bone marrow and one idiopathic thrombocytopenia. In all of these cases infusions of toluidine blue stopped the bleeding. Twenty-one patients with bleeding tendencies had a negative toluidine blue titration. The platelet count varied from very low to normal. No response occurred with toluidine blue when given.

The administration of toluidine blue was effective in stopping bleeding in cases in which the presence of heparin-like material was proven in the blood stream.

CHEMICAL DETERMINATION OF URINARY CORTICOSTEROIDS. *B. N. Horwitt* and A. Segaloff.* Endocrine Research Laboratory, Alton Ochsner Medical Foundation, and the Department of Medicine, Tulane University, New Orleans, La.

A number of methods have been described for the chemical determination of corticosteroids in urine. One of these depends on the periodic acid oxidation of the alpha ketol side chain common to many of the adrenal steroids and all of the active adrenal steroids. Another chemical method depends on the reaction of phenylhydrazine in H_2SO_4 with 17,21-dihydroxy-20-keto steroids.

A study has been made of the relative merits of these two methods. Simultaneous experiments were conducted to determine whether methods of extraction could be devised to subdivide the corticosteroids into total, free and conjugated forms. This fractionation was carried out by extracting urinary aliquots with chloroform, butyl alcohol or both. In addition an enzymatic hydrolytic procedure which was developed in this laboratory was employed, using a bacterial preparation of β-glucuronidase followed by extraction with chloroform. This not only gave higher values than the usual hydrolysis at pH 1 but also resulted in lower blanks and colors which more closely resemble the standards. The periodic acid oxidation method appears to be more reliable than the phenylhydrazine-H_2SO_4 method for use with urinary extracts.

PLASMA LEVELS AND RELEASE OF LYSOZYME FROM TUBERCULIN-INJURED LEUKOCYTES OF TUBERCULOUS AND NON-TUBERCULOUS HUMANS. *Grace P. Kerby and S. N. Chaudhuri,** Department of Medicine, Duke University School of Medicine, Durham, N. C.

By a method of detection of cell injury which depends on the release of intracellular substances from injured cells into the surrounding medium, the effect of tuberculin and of staphylococcal toxin on human leukocytes from tuberculous and non-tuberculous subjects has been studied. The substance measured was a lysozyme-like enzyme.

No significant difference between the leukocytes from tuberculous and non-tuberculous subjects ($p = >0.05$) could be detected by the degree of injury resulting from two hours of

in vitro exposure of leukocytes to tuberculin (PPD, final dilution 15 γ/ml.) or to staphylococcal toxin. In the presence of these substances, as well as in control experiments, there was evidence of greater lysozyme activity with leukocytes from tuberculous subjects than from non-tuberculous subjects—controls 36 per cent ± 8 (tuberculous), 31 per cent ± 10 (non-tuberculous), the difference being of possible significance ($p = < 0.05$). This was found to be due not to a difference in the amount of lysozyme released from the leukocytes but to an artefact resulting from a significantly greater lysozyme activity ($p = < 0.01$) in the 10 per cent autologous plasma which was added to the leukocytes of tuberculous subjects as compared to that from non-tuberculous subjects.

FURTHER STUDIES ON THE HYPERGLYCEMIA FACTOR OF THE PANCREAS. *Robert F. Kibler* and J. D. Myers*, Department of Medicine, Duke University School of Medicine, Durham, N. C.

In a previous report it was demonstrated that an increase in net splanchnic glucose production (NSGP) accounts for the hyperglycemic effects of pancreatic hyperglycemic factor (HGF) in man. Further studies have shown that: (1) HGF by continuous intravenous infusion over a two to three and a half hour period in normal man produces a sustained outpouring of glucose from the liver with hyperglycemia. (2) Gluconeogenesis from protein, as measured by splanchnic urea production, does not contribute significantly to the increased NSGP after HGF. (3) In a group of eighteen patients with moderate to severe parenchymatous liver disease the hyperglycemic response to HGF was very significantly reduced. This response gave better correlation with the actual pathologic process in the liver than did conventional liver function tests. (4) Five patients with complete obstructive jaundice and one patient with cholangiolitic hepatitis gave essentially normal responses to HGF.

It has been suggested that HGF may play a role in the rebound of blood glucose from insulin hypoglycemia. The classic concept assigns this role to epinephrine. However, dihydroergotamine, in doses which effectively block hyperglycemia from moderate intravenous doses of epinephrine, does not prevent the rebound in NSGP from mild insulin hypoglycemia. This observation fits with the concept that some factor other than epinephrine produces this rebound phenomenon; HGF is one of several possibilities for its explanation.

EFFECTS OF COMPOUNDS A, E AND F ON EXPERIMENTAL VIRAL INFECTION. *Edwin D. Kilbourne*, Division of Infectious Disease, Department of Medicine, Tulane University School of Medicine, New Orleans, La.

Previous studies from this laboratory have demonstrated the paradox of increased virus multiplication and prolonged survival in chick embryos injected with compound E (cortisone). It has been established that the divergent effects of cortisone on viral increase and host survival are separable by proper timing of cortisone administration. Specifically, injection of cortisone prior to virus inoculation results in maximally increased virus and earlier death; simultaneous injection of cortisone and virus in the paradox of increased virus and prolonged survival; injection of cortisone eighteen to forty-two hours after virus in no viral increase and still longer survival. Studies of the related corticosteroids compound A (11-dehydrocorticosterone) and compound F (17-hydroxycorticosterone) have demonstrated inhibition of embryo growth and increased rates of Lee virus multiplication comparable to those observed with compound E. Viral concentrations four to sixteen times those of control eggs were demonstrable in different experiments by the hemagglutination technic. Of the three compounds, A has the greatest and F the least effect on embryo growth as measured by wet and dry weight determinations. There has been no observed correlation between growth inhibition and viral increase. Under the experimental conditions employed it has not been possible to increase the survival time of virus-infected embryos with either compound A or F. The parallelism of action of compound A and the steroids therapeutically active in man is of theoretical interest and is being explored further.

INTERACTION OF SERUM WITH THE LEUKOCYTE INHIBITOR OF DESOXYRIBONUCLEASE AND THE LUPUS ERYTHEMATOSUS CELL PHENOMENON. *N. B. Kurnick*, Department of Medicine, Tulane University School of Medicine, New Orleans, La.

Recently Kurnick, Schwartz, Pariser and Lee reported that extracts of human leukocytes which contain a specific desoxyribonuclease (DNase) inhibitor are capable of suppressing the lupus erythematosus (L. E.) cell phenomenon which is characterized by depolymerization

of desoxyribonucleic acid. The interactions of the inhibitor with human sera and serum fractions were studied in an attempt to elucidate the role of the inhibitor in the L. E. phenomenon. It was found that the inhibitor was destroyed upon incubation with whole normal or L. E. serum but not on incubation with Cohn's Fraction II prepared from these sera. Dialyzed Fraction II from L. E. serum is not capable of eliciting the L. E. cell phenomenon with washed white blood cells but does elicit the phenomenon if *normal* serum is added. Since the inhibitor is destroyed by proteolytic enzymes, which are present in whole serum but not in Fraction II, it is probable that the observed effects of whole serum on the inhibitor are due to the normally occurring proteolytic enzymes.

It is suggested that the factor in Fraction II from L. E. serum, which is capable of eliciting the L. E. cell phenomenon, may act indirectly by favoring the penetration into the leukocytes of proteolytic enzymes normally present in serum. These enzymes, then, destroy the DNase inhibitor, permitting the action of DNase.

INVESTIGATION OF A CALCIUM INFUSION TECHNIC IN THE STUDY OF METABOLIC BONE DISEASE. *Laurence H. Kyle, Leonard A. Erdman* and Marcus Schaaf,** Department of Medicine, Georgetown University School of Medicine and Georgetown University Hospital, Washington, D. C.

The mineral alterations which follow the infusion of calcium have been studied in a number of patients with and without metabolic bone disease. Blood and urinary calcium and phosphorus, as well as endogenous creatinine clearance, were measured before, during and after the intravenous administration of calcium gluconate. Patients were maintained on a constant intake of calcium and phosphorus during the entire test. Urinary collections were made for periods of twenty-four hours and during a portion of the day of infusion, collection periods were of one or two hours' duration. A constant pattern of change was observed in patients without bone disease. Serum calcium rose sharply during the infusion and about 60 per cent of the infused calcium was retained. Urinary phosphorus excretion decreased during the infusion and in most instances decreased phosphate excretion was reflected in the twenty-four-hour collection period. Serum phosphorus increased approximately 40 per cent and remained elevated for several hours.

Indication that hypercalcemia results in diminution of parathyroid activity is provided by elevation of serum phosphorus in the face of decreased urinary phosphate excretion. In two patients with hypoparathyroidism marked increase in phosphorus excretion accompanied the infusion of calcium. In one instance of functioning parathyroid tumor there was minimal rise in serum phosphorus and no diminution of phosphate excretion. Although very large amounts of the infused calcium were retained in osteomalacia, patients with osteoporosis demonstrated a degree of calcium excretion comparable with that which occurs in normal persons.

These data indicate that application of the calcium infusion technic may be of value in the study of bone physiology and helpful in the investigation of metabolic bone disease.

RENAL HEMODYNAMIC EFFECTS OF ARAMINE. *W. R. Livesay* and John H. Moyer*, Departments of Medicine and Pharmacology, Baylor University College of Medicine, and the Cardiac Clinic of Jefferson Davis Hospital, Houston, Tex.

Nor-epinephrine, a peripherally acting vasopressor agent, is an effective drug for the treatment of normal volemic shock but there is some evidence to indicate that renal vasoconstriction may accompany administration of this drug. Aramine (a monohydroxyphenylalkylamine) is also a potent peripheral acting vasopressor agent but the renal hemodynamic effects have not been studied. Therefore a comparative study on the renal hemodynamic response to nor-epinephrine and aramine was made. Glomerular filtration rate (GFR) was measured with inulin and renal plasma flow (RPF) was determined by para-aminohippurate clearance. Both nor-epinephrine and aramine were administered by continuous intravenous infusion to normal individuals. Simultaneous electrocardiograms were recorded.

The vasopressor action of aramine became manifest within ten minutes after the infusion was started and lasted fifteen to forty minutes after the infusion was discontinued, in contrast to the evanescent action of nor-epinephrine. It was found that, with an average increase in mean blood pressure to 150 per cent of the control values for eight normal subjects, there was an average decrease in RPF to 85 per cent of the control. The reduction in RPF was associated with a slight increase in GFR and

urine volume. The renal hemodynamic effects of nor-epinephrine were more pronounced. In eleven normal patients given nor-epinephrine infusion it was found that, with an average mean blood pressure of 136 per cent of the control level, there was a decrease in RPF to 60 per cent of the control. However, urine volume and GFR were not significantly altered.

It is concluded that with similar degrees of pressor action aramine produces less renal vasoconstriction than does nor-epinephrine.

EFFECTS OF GLUCOSE AND FRUCTOSE ON AEROBIC GLYCOLYSIS OF HUMAN LEUKOCYTES *in vitro*. *Gordon R. McKinney, Samuel P. Martin and Rosalie Green (introduced by R. Wayne Rundles)*, Departments of Medicine and Physiology and Pharmacology, Duke University School of Medicine, Durham, N. C.

Leukocytes were separated from the blood of healthy individuals without exposing the cells to wettable surfaces, anticoagulants or excessive gravitational force and suspended in plasma diluted 1:5 with Hanks' solution for metabolic studies.

The aerobic formation of lactate by intact cells was greater from glucose than from an equal concentration of fructose: 100 mg. per cent (final concentration) glucose yielded +0.740 (±0.107 s.e.) μ mols of lactate per ten million leukocytes per hour, whereas 100 mg. per cent fructose gave +0.469 (±0.06 s.e.) μ mols. Below physiologic levels lactate production was proportional to the amount of added glucose but above 80–100 mg. per cent the rate declined. However, lactate formation with fructose increased directly until the concentration reached 300 mg. per cent. When the two sugars were present together and the final concentration of each was 100 mg. per cent, the yield of lactate was equal to the sum of either alone. With broken cells aerobic glycolysis proceeded similarly with glucose or fructose, and the relationship of lactate production to increasing concentrations of either hexose was qualitatively similar to that of intact cells in the presence of glucose.

These data indicate the existence of two separate, non-competing mechanisms whereby glucose and fructose enter the normal human leukocyte. The greater utilization of glucose by the intact cell may indicate active absorption whereas fructose may diffuse passively into the cell.

CONTINUOUS ACTH THERAPY OF CHRONIC GLOMERULONEPHRITIS WITH NEPHROTIC EDEMA. *Arthur J. Merrill*, Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

Six patients with chronic glomerulonephritis and nephrotic edema have been treated for two to eight months with a new continuous method of ACTH GEL administration. All except one patient had had three to ten ten-day intermittent courses of treatment followed by continued albuminuria and relapse into the edematous state. Duration of the disease varied from one to twenty months. Two patients had beginning nitrogen retention and all had considerable albuminuria and edema. The patients were from nine months to four years of age. With some initial variations each was given an appropriate dose once daily until either free of albuminuria and hematuria or until a steady state of mild albuminuria was achieved. Then they were abruptly changed to ACTH GEL every other day and the dose reduced gradually. All have been free of edema since institution of this schedule whereas they had fluctuated between edematous and dehydrated states with intermittent courses. Five have been without albuminuria for significant periods, except for occasional relapses accompanying colds or too rapid reduction of dose. These relapses were abolished promptly by temporarily increasing the dose. The sixth patient is clinically well but has a very faint trace of albuminuria. All have been normally active after a brief initial period.

ANTIDIURETIC SUBSTANCES IN BLOOD AND PLASMA OF PATIENTS WITH CONGESTIVE HEART FAILURE AND CIRRHOSIS. *George L. Mitchell, Jr.,* Francis W. Fitzhugh, Jr.,* Oscar W. Freeman* and Arthur J. Merrill*, Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

A study was undertaken in order to determine: (1) if excess antidiuretic substances are present in the blood of patients with congestive heart failure or cirrhosis; and (2) the organ of origin of such substances.

To avoid extraneous substances produced by chemicals when added to blood and the pitfalls of antidiuretic assays on the urine, approximately 500 ml. of whole fresh antecubital vein blood or approximately 50 ml. of fresh internal jugular vein plasma were transfused rapidly into normal individuals in a state of water diuresis. Eleven studies using whole blood and

ten studies using jugular plasma were done. The donor group consisted of six convalescent patients without edema, nine patients with chronic congestive heart failure and four patients with Laennec's cirrhosis. Urine flow studies and electrolyte excretion determinations were made in all recepients and renal clearance studies were carried out on those receiving whole blood.

Blood or plasma from five of six controls were without antidiuretic effect while that from six of nine cardiac patients caused antidiuresis. The blood or plasma from three of four cirrhotic patients showed no antidiuretic effect.

Our results indicate that an antidiuretic substance, presumably of posterior pituitary origin, is present in the blood of patients with congestive heart failure. The effects of jugular plasma were greater than those of peripheral blood. Further studies must be done with blood from cirrhotic patients. No evidence of other humoral substances affecting electrolyte excretion or renal clearance was found.

RESULTS OF THERAPY WITH DIBENZYLINE IN HYPERTENSION COMPARED WITH OTHER AUTONOMIC BLOCKING AGENTS. *John H. Moyer, Sam I. Miller* and Ralph V. Ford,** Department of Pharmacology, Baylor University College of Medicine, Houston, Tex.

Dibenzyline (N-phenoxyisopropyl-N-benzyl-β-chlorethylamine) administered orally has been used in the treatment of thirty-two patients with severe essential hypertension; 72 per cent responded with more than a 20 mm. Hg fall in mean blood pressure. In the standing position the blood pressure decreased to less than 150 mm. Hg systolic and 100 diastolic in 47 per cent of the patients. There was a high incidence of side effects, particularly tachycardia, and those related to the brain and gastrointestinal tract. Only 34 per cent of the patients felt sufficiently benefited to continue therapy for more than three months.

Cerebral blood flow studies using the nitrous oxide method in the supine position showed no alteration in cerebral hemodynamics associated with reduction in blood pressure. Renal hemodynamic studies failed to show any alteration in the supine position. A comparison with other autonomic blocking drugs used in the same clinic indicates that the ganglionic blocking drug, hexamethonium, is the agent of choice when the drugs are administered orally.

EXCESSIVE LOSS OF PROTEIN AND NITROGEN IN PERITONEAL FLUID DURING PERITONEAL IRRIGATION OF NEPHRECTOMIZED DOGS. *E. E. Muirhead, F. Jones,* J. A. Stirman* and W. Lesch,** Department of Pathology, Southwestern Medical School of the University of Texas, Dallas, Tex.

The protein and total nitrogen content of the outflow fluid during peritoneal irrigation was determined in fourteen and sixteen dogs, respectively, (weight 8–19 kg.) up to fifteen days after bilateral nephrectomy. The fluid protein concentration remained fairly constant within certain ranges, seeming to be an individual dog characteristic. The ranges were 1–3 gm./L. in four, 3–6 gm./L. in six, 4–9 gm./L. in three and 8–12 gm./L. in one dog. The plasma protein concentration decreased by an average of 1.2 gm./100 cc.

Preliminary observations indicate a decrease in the ratio of plasma: peritoneal fluid concentration of alpha, beta and gamma globulins, fibrinogen and albumin, resulting from no change or slight increase in plasma globulins and a decrease in plasma fibrinogen and albumin, plus an increase in fluid globulins and no change or increase in fluid fibrinogen and albumin. The total nitrogen concentration remained within certain ranges: 1–3 gm./L. in two, 1–7 gm./L. in two, 3–7 gm./L. in eight, 1–9 gm./L. in three dogs and 5–12 gm./L. in one dog. The total nitrogen loss varied between 50 and 211 gm. (average 118 gm.) in ten days.

After nephrectomy dogs maintained by peritoneal irrigation lose large quantities of plasma proteins and nitrogen in the irrigating fluid.

EFFECTS OF PRESSOR AND DEPRESSOR AGENTS AND INFLUENCES ON PULMONARY AND SYSTEMIC PRESSURES OF NORMOTENSIVE AND HYPERTENSIVE SUBJECTS. *R. A. Nelson,* L. G. May,* Alene Bennett,* Mitsu Kobayashi* and Raymond Gregory,* John Sealy Memorial Laboratory for Clinical Research, and the Department of Internal Medicine, University of Texas School of Medicine, Galveston, Tex.

A study was made of the mechanism which spares the pulmonary circulation in essential hypertension, which may be due to absence of pulmonary vasoconstrictors or to selective systemic vasoconstriction. The effects on systemic and pulmonary pressures of six pressor agents, including angiotonin, psychogenic pressor effects under hypnosis, cold pressor action and four depressor agents were studied in twenty-

two hypertensive and normotensive subjects using pulmonary arterial catheterization. Systemic pressure elevation caused by angiotonin and other pressor agents, except pitressin, was accompanied by a corresponding pulmonary elevation. This is unlike essential hypertension. The PAm-PCm gradient was unchanged during pulmonary pressure elevations. No correlation between pulmonary pressure changes and known effects of these agents on cardiac output was observed. Pitressin and psychogenic pressor effects under hypnosis produced systemic hypertension acutely without associated pulmonary hypertension. Systemic and pulmonary pressures dropped with the depressor agents.

Our results suggest that angiotonin and other pressors used are not the substances which cause systemic hypertension (without pulmonary hypertension) in essential hypertension. Results with pitressin, however, indicate that at least one naturally occurring substance is capable of selectively raising the systemic pressure. Centrally induced hypertension also selectively elevated the systemic pressure. Pulmonary arterial and venous constriction are believed to be caused by the pressor agents used.

CLINICAL AND SEROLOGIC OBSERVATIONS ON FIVE CASES OF HISTOPLASMOSIS. *R. T. Parker,* W. T. Raby,* J. B. Workman* and T. E. Woodward*, Section of Infectious Diseases, Department of Medicine, University of Maryland School of Medicine, Baltimore, Md.

Five cases of pulmonary infiltration secondary to Histoplasma capsulatum infections have been observed for periods ranging from three to four years. Although the inciting organism was not isolated in any case, serologic diagnosis was established in all instances. A wide range in severity of clinical signs and symptoms was noted. Despite widespread pulmonary lesions which progressed to calcification no alteration in pulmonary function was demonstrable. Epidemiologic studies upon four of these cases occurring in one family limited the source of infection to a rural chicken house. To our knowledge this is the first published report suggesting that histoplasmosis is endemic in Maryland.

EFFECT OF VARIOUS ANTIBIOTICS AND CORTISONE UPON BOTULINUM, TETANAL AND DIPHTHERIAL TOXINS *in Vivo*. *R. T. Parker, M. J. Snyder and A. M. Merideth, (introduced by Theodore E. Woodward)*, Section of Infectious Diseases, Department of Medicine, University of Maryland School of Medicine, Baltimore, Md.

The efficacy of penicillin and several streptomyces-derived antibiotics in the treatment of certain infections is now well established. However, little is known regarding the effect of such drugs upon the toxemia of these infections. Accordingly, aureomycin, chloramphenicol, neomycin, penicillin, streptomycin and terramycin were used in the therapy of botulinum, tetanal and diphtherial intoxications of laboratory animals to determine if any beneficial or deleterious alteration in the course of these entities could be produced.

Mice given minimal amounts of purified botulinum and tetanal toxins and treated with the maximal tolerated quantities of the aforementioned drugs showed no alteration of response compared with control mice receiving toxin alone. Furthermore, these antibiotics did not affect diphtherial intoxication in guinea pigs. Cortisone has been shown to exert an ameliorating effect upon the toxemia of patients with typhoid fever and pneumonia. However, in mice and guinea pigs administration of this corticoid did not alter the effect of diphtherial, tetanal and botulinum toxins.

TREATMENT OF ACUTE CEREBRAL VASCULAR ACCIDENTS. *John L. Patterson, Jr., Albert Heyman and Louis L. Battey,** Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

Blood flow through the brain (CBF) has been found decreased in patients with cerebral vascular accidents (CVA). In order to determine their therapeutic value vasodilator agents known to increase CBF were studied in control subjects and patients with CVA. Intravenous administration of 600 to 900 cc. of 3 per cent $NaHCO_3$ in five patients with CVA produced moderate increases in CBF without definite clinical improvement. In contrast 3 per cent $NaHCO_3$ or 500 cc. of ½ molar sodium lactate produced marked increases in CBF in normal subjects. Inhalation of 5 per cent CO_2, known to increase CBF, caused excessive dyspnea and hypertension in patients with CVA. Carbon dioxide in 3.5 per cent concentrations was usually well tolerated and produced a slight increase in CBF and decreased A-V oxygen difference in control subjects. Seven of twelve patients with CVA given 2.5–3 per cent CO_2 appeared to have improvement in muscle strength, coordina-

tion and speech during thirty to sixty minutes of inhalation.

It is suggested that diseased cerebral vessels may be less responsive than normal vessels to intravenous $NaHCO_3$. Low concentrations of CO_2 may have effects on cerebral function other than vasodilation and appear worthy of trial in patients with CVA, particularly in those with marked hyperventilation.

DYNAMICS OF THE RELAXATION PHASE OF THE HUMAN HEART. *J. Rush Pierce (introduced by T. R. Harrison)*, Department of Internal Medicine, Medical College of Alabama, Birmingham, Ala.

Studies have been made of various physiologic events as measured by the carotid and jugular pulses, heart sounds, ballistocardiogram, electrocardiogram and precordial pulse tracings. The results are outlined:

	Protodiastole	Early Isometric Relaxation	Late Isometric Relaxation
Carotid and jugular	Sudden fall to the incisural notch		Rising to the jugular V wave
BCG	Headward	Footward	Headward
EKY—posterior basal left ventricle	Either in or out	Outward	Outward
EKY—right ventricle	Outward	Inward	Inward
EKY—right auricle	Outward	Inward	Inward
Precordial movements	Outward	Inward except at apex	Either in or out

These findings can be partially explained by assuming that the cardiac muscle bundles relax in an orderly sequence. Relaxation probably first begins in the lower interventricular septum, papillary muscles and apices of both ventricles. As the major part of the superficial muscles relax there is elongation of the heart with counterclockwise rotation. It seems likely that the deep muscle bundles relax last, during the latter half of isometric relaxation.

EFFECT OF POTASSIUM DEPLETION IN ESSENTIAL HYPERTENSION. *Arthur Ruskin and Belle Ruskin (introduced by Raymond Gregory)*, Department of Medicine, University of Texas, Medical Branch, Galveston, Tex.

Study of the relation of potassium availability to clinical hypertension is justified by: (1) reciprocal relations of serum sodium and potassium in adrenocortical hyper- and hypoactivity, with corresponding arterial hyper- and hypotension; (2) the hypotensive effects of sodium depletion (Ruskin et al., 1952) and of potassium depletion in experimental animals (Friedman et al., 1951); (3) the insufficiently studied possible intermediation of hypopotassemia in the hypotensive action of KCNS (Ruskin and McKinley, 1947).

In a study over a period of months potassium depletion was accomplished in twelve cases of uncomplicated essential hypertension by means of: (1) a low potassium diet; (2) oral administration of 60–120 gm. daily of a potassium-free cation exchange resin (Win 3,000); and (3) rare injections at two- to three-day intervals of 2 cc. of mercaptomerin. The arterial pressures fell 30 mm. systolic and 20 mm. diastolic in the majority of cases, parallel to the developing hypopotassemia which fell as low as 2.5 to 3.0 mEq./L. The severer hypertensives were in general more resistant. Sodium intake as high as 575 mEq./day or as low as 18 mEq./day did not alter the arterial pressure or the hypokalemic effects of potassium depletion.

CEREBRAL CIRCULATION AND METABOLISM IN CHRONIC PULMONARY DISEASE WITH OBSERVATIONS ON THE EFFECTS OF MILD EXERCISE. *P. Scheinberg, J. Blackburn,* M. Rich* and M. Saslow,** Department of Physiology, University of Miami School of Medicine, Coral Gables, Fla.

Chronic pulmonary disease produces variable alterations in blood O_2 and CO_2 tensions. Changes in these gas-tensions are known to influence cerebral circulation and metabolism profoundly in acute experiments. Cerebral blood flow and metabolism were measured by the original nitrous oxide technic in thirteen subjects and by the integrated sampling technic modification in nine other subjects with chronic pulmonary disease before and during mild exercise. These patients were not studied until they had achieved a stable clinical state.

There were no significant changes from normal in cerebral blood flow, oxygen consumption or vascular resistance, although per cent arterial oxygen saturation, arterial pO_2 and CO_2 content were altered from normal. There was a satisfactory correlation between cerebral blood flow and pCO_2, and between cerebral vascular resistance and pCO_2, but none between pO_2 and cerebral blood flow or per cent arterial oxygen saturation and cerebral blood flow. Mild exercise produced no changes in cerebral metabolic functions. There were no

significant differences in cerebral vascular or metabolic functions in the two groups measured by the different nitrous oxide technics. Electroencephalograms on eight of the subjects were all within normal limits.

GASTRIC FUNCTION AND THE SELECTION OF THE SURGICAL PROCEDURE OF CHOICE IN PEPTIC ULCER. *Arthur M. Schoen* (*introduced by J. M. Kinsman*), Departments of Surgery and Medicine, University of Louisville School of Medicine, Louisville, Ky.

Surgery for peptic ulcer is intended to depress gastric acidity and motility. Gastroenterostomy with either partial gastrectomy or vagotomy usually produces these changes. Gastric function is regulated principally by the humoral and vagal phases, and removal of the predominant phase would be expected to reduce gastric activity more than removal of the subordinate phase.

Detailed studies of gastric function have been made by use of an experimental method which utilizes the principle of dilution and emptying of an identifying test meal. Rates of secretion and emptying are calculated by formulas. The accuracy of the method is about 94 per cent. The gastric response to maximal histamine and to insulin hypoglycemia stimulation has been measured. A greater response to histamine is designated as predominantly humoral, and a greater insulin response as predominantly vagal. Preoperative studies on 100 persons with peptic ulcer indicated sixty-five predominantly vagal, and these subsequently had vagotomy; twenty-nine were humoral and had subsequent partial gastrectomy; and nine were equal, six having subsequent partial gastrectomy and vagotomy, and three gastrojejunostomy alone.

During a six and a half year follow-up period there have been three recurrences after complete vagotomy, one after partial gastrectomy, one after combined gastrectomy and vagotomy, and one after gastrojejunostomy.

EFFECT OF ACTH AND CORTISONE ON THE COURSE OF DISSEMINATED LUPUS ERYTHEMATOSUS. *Theodore B. Schwartz*, Department of Medicine, Duke University School of Medicine, Durham, N. C.

Twenty patients with disseminated lupus erythematosus (L. E.) have been observed over periods ranging from one to twenty-eight months. Of the eleven patients who still survive, nine are in remission. The following observations are emphasized: (1) L. E. may present itself as a chronic disease; five patients have lived more than six years after onset. (2) One-fourth of the group spent 35 to 93 per cent (mean 67 per cent) of the time prior to hormonal therapy in remission. (3) In forty of forty-eight (85 per cent) courses of ACTH or cortisone therapy, a favorable initial response occurred and the disease was initially modifiable in 90 per cent of the patients. (4) No patient with active L. E. has lived longer than one month after becoming unresponsive to hormonal therapy. (5) Of the seven patients observed at the time of death uremia appeared to be the major contributing factor in five. (6) Secondary infection occurred in 80 per cent of the patients and in 70 per cent the urinary tract was involved. Prior to therapy the patients spent 37 per cent of their time in remission; after institution of therapy, 80 per cent. Despite occasional wide variations, it seems justifiable to conclude that ACTH and cortisone therapy has significantly contributed to the maintenance of remission in these patients.

COMPARATIVE EFFECTS OF L-NOR-EPINEPHRINE, SYNTHETIC L-EPINEPHRINE, AND U.S.P. EPINEPHRINE UPON CEREBRAL BLOOD FLOW AND METABOLISM IN MAN. *Willis Sensenbach, Leonard Madison and Lamar Ochs* (*introduced by Andres Goth*), Department of Medicine, Southwestern Medical School of the University of Texas, and the Department of Medicine, Veterans Administration Hospital, Dallas, Tex.

The effect of the intramuscular administration of L-nor-epinephrine, synthetic L-epinephrine and U.S.P. epinephrine upon cerebral circulatory and metabolic functions in normal healthy males has been determined by the nitrous oxide technic for the measurement of cerebral blood flow. The studies were made in the following manner: immediately after a control cerebral blood flow determination L-nor-epinephrine, synthetic L-epinephrine or U.S.P. epinephrine in oil was administered intramuscularly in amounts varying from 600 μg. to 1,400 μg.; fifteen to twenty minutes later the experimental blood flow measurement was made. Studies that have been made in a total of forty-one subjects, thirteen of whom received L-nor-epinephrine, thirteen, synthetic L-epinephrine and fifteen, U.S.P. epinephrine.

The data show that L-nor-epinephrine is a potent cerebral vasoconstrictor. Mean CBF was

reduced 21 per cent owing to a disproportionate increase in mean CVR (64 per cent) above mean MABP (31 per cent). Mean $CMRO_2$ was unaltered because of a compensatory increase in mean arteriocerebral venous oxygen difference. Synthetic L-epinephrine, in contrast to L-nor-epinephrine, had no significant effect upon cerebral hemodynamics or metabolism. The sole change of significance was a small reduction in mean MABP. The cerebrovascular effects of synthetic L-epinephrine and U.S.P. epinephrine contaminated with nor-epinephrine are identical.

STUDIES ON THE CONTRACTILE PROTEINS OF HEART MUSCLE. *Max Taeschler* and R. J. Bing*, Departments of Medicine and Physiology, Medical College of Alabama, Birmingham, Ala.

Some of the physiologic properties of the contractile proteins, actomyosin, have been studied on the extracted heart muscle preparation of the dog. Contractions could be elicited only with adenosinetriphosphate (ATP) but not with electric stimuli, epinephrine or acetylcholine. This indicated that the normal physiologic mechanism of excitation had been lost and that the contraction process was initiated by direct interaction between ATP and the contractile proteins.

As with fresh muscle the speed of contraction decreased with increased load; the work of the isotonically contracting preparation increased with rising tension and decreased after an optimal load was exceeded. Prolonged stretch during the extraction, leading to increased fiber length, resulted in greater work of the extracted muscle preparation. Extracted heart muscle strips prepared from hearts of dogs in acute failure performed less work than strips obtained from hearts of normal animals.

The essential similarities between extracted and fresh heart muscle suggest that many of the physiologic properties of fresh heart muscle are due to inherent qualities of the contractile proteins.

COMPARATIVE EFFECTS OF PRESSOR AND DEPRESSOR SUBSTANCES ON PULMONARY VASCULAR PRESSURES OF NORMOTENSIVE AND EXPERIMENTAL HYPERTENSIVE DOGS. *A. P. Thaddeus,* L. G. May,* Alene Bennett,* Mitsu Kobayashi* and Raymond Gregory*, Department of Internal Medicine, University of Texas School of Medicine, Galveston, Tex.

Pulmonary artery pressure is normal in essential hypertension. The pulmonary pressure responds as does the systemic pressure to several pressor and depressor agents in normotensive and hypertensive individuals. Vasoconstriction in the pulmonary vascular system and back pressure from a failing left ventricle have been proposed as possible mechanisms by which epinephrine increases pulmonary pressure.

Pulmonary arterial (PA), pulmonary "capillary" (PC), and pulmonary "end" vein (PVC) pressures were measured in ten normotensive and four experimental renal hypertensive dogs. Chromatographically purified angiotonin, epinephrine and nor-epinephrine increased all of these pressures. Tetraethylammonium bromide and theophylline ethylenediamine decreased these pressures.

PAm, PCm and PVCm elevations may be due to arteriolar constriction and venous constriction of the pulmonary circulation. Right atrial, superior and inferior vena caval pressures were measured and the response to pressor and depressor agents was the same as that of the pulmonary circulation. The pressure in the inferior vena cava always rose before and to a greater degree than the right atrial or superior vena caval pressures (two dogs).

We conclude that the increased systemic venous pressure is due to venoconstriction and not to right ventricular failure, and that increased pulmonary arterial and venous pressures following pressor agents is due to vasoconstriction rather than to left ventricular failure. The invariable decrease in PAm and PCm following tetraethylammonium bromide and theophylline ethylenediamine must be ascribed to vasodilation rather than to any change of left ventricular function.

RADIORUBIDIUM (Rb^{86}) AS A TRACER OF POTASSIUM IN MAN WITH AND WITHOUT CHRONIC CONGESTIVE HEART FAILURE. *S. A. Threefoot, C. T. Ray and G. E. Burch*, Department of Medicine, Tulane University School of Medicine, New Orleans, La.

The short half-life of K^{42} makes it unsuited for the study of potassium metabolic phenomena over prolonged periods. Because of the chemical, physiologic and pharmacologic similarities of Rb and K, Rb^{86} was used alone and simultaneously with K^{42} to investigate the reliability of Rb^{86} as a tracer of potassium. Studies were made in subjects with and without congestive heart failure under metabolic balance studies

which included measurements of Cl, Na, K and water.

In simultaneous studies of the rapid transfer of Rb^{86} and K^{42} in plasma, erythrocytes and whole blood, the two isotopes showed indistinguishable turnover rates. The transfer rates of Rb^{86} and K^{42} are quantitatively defined in these studies, being the same for the controls and the patients with heart failure. The biologic half-life of Rb^{86} measured for the plasma, erythrocytes and whole blood was found to be approximately thirty days in all subjects. A study of renal potassium metabolic phenomena obtained from urinary excretion and K and Rb^{86} clearance rates revealed qualitative similarities but quantitative differences between K and Rb^{86}.

These data indicate that Rb^{86} can serve useful purposes in a study of potassium metabolic phenomena requiring prolonged observation and that Rb^{86} enters in the potassium metabolic pool in spite of differences in their behavior.

STUDIES OF HUMAN SERUM FOLLOWING ORAL ADMINISTRATION OF VITAMIN B_{12}. *W. G. Unglaub,* H. L. Rosenthal* and G. A. Goldsmith*, Department of Medicine, Tulane University School of Medicine, New Orleans, La.

Mean vitamin B_{12} activity in serum in thirty normal subjects was 0.20 mμg./ml. (range 0.08 to 0.42); in subjects with macrocytic anemias values ranged from 0 to 0.08 mμg./ml.

Following oral administration of vitamin B_{12} the changes in serum levels of normal subjects were as follows: after 3,000 μg. moderate increases in three (to 0.90, 0.75, and 0.68 mμg./ml.), slight increases in two (to 0.59 and 0.56 mμg/ml.) and no change in one; after 1,000 μg. slight increases of doubtful significance in two subjects; after 500 μg. no significant increase in two subjects.

In patients with pernicious anemia the following changes were observed: after 3,000 μg. a marked increase in one subject (0.02 to 1.54 mμg./ml.) and a moderate increase in another (0.05 to 0.46 mμg./ml.); after 1,000 μg. a marked rise in one subject (0.01 to 0.83 mμg./ml.); after 500 μg. a slight rise (0.07 to 0.32 mμg./ml.) in one of two subjects. Single doses of 3,000 μg. stimulated a marked hematologic response. Doses of 1,000 μg. and 500 μg. were less satisfactory. Administration of vitamin B_{12} in ten hourly doses of 50 μg. resulted in a slight increase in serum levels in one patient with pernicious anemia and no significant increase in one normal subject.

EFFECT OF SURFACE ON THE DIRECT BALLISTOCARDIOGRAM. *Rhett P. Walker (introduced by T. R. Harrison)*, Department of Internal Medicine, Medical College of Alabama, Birmingham, Ala.

The effect of surface on the direct ballistocardiogram has been studied. Certain healthy young adults whose ballistocardiograms had an abnormal oscillatory pattern when recorded on a hard, flat surface became normal when placed in a sand bed. Changes in the ballistocardiographic pattern were observed in some subjects when they folded their arms while lying on the hard, flat surface, thus changing their points of suspension. When lying in sand folding of the arms did not cause significant changes. The vibratory motion of cadavers studied on several types of surfaces demonstrated that sand had two effects: it produced a definite damping and tended to increase the vibratory frequency of the body.

It was shown that the commercial coil magnet pickup with 25 microfarad capacitor produces a tracing which is a mixture of velocity and displacement. A bellows air-conduction system was designed and built which is quite satisfactory for the recording of the displacement ballistocardiogram.

It seems apparent from these observations that considerable caution should be used in the interpretation of the direct ballistocardiogram until the extrinsic factors which may modify it have been minimized.

DOUBLE SYSTOLIC MURMUR IN INTERVENTRICULAR SEPTAL DEFECT. *Kathryn W. Willis (introduced by T. R. Harrison)*, Department of Internal Medicine, Medical College of Alabam, Birmingham, Ala.

An adult patient with a loud systolic murmur as the result of an interventricular septal defect has been studied with sound tracings, ballistocardiograms, electrokymograms and precordial pulsations as well as intracardiac catheterization.

Sound tracings recorded from the second, third and fourth interspaces at the left sternal margin reveal certain consistent variations in the character of the murmur which suggest alternating right to left and left to right shunts of blood. Oxygen saturation of ventricular blood supports the assumption that both types of

shunt exist. The murmur begins with but does not completely mask the first sound in all areas. In the initial phase of the murmur (during isometric systole) the intensity is low and becomes markedly accentuated with ejection systole. There is another break in the intensity of the murmur about the peak of the carotid pulse tracing such that the murmur may at times have a double crescendo-decrescendo appearance within the phase of systole. The second sound is masked by the murmur which appears to extend into protodiastole.

Correlations of the murmur with the right and left ventricular pressure curves, electrokymograms and records of precordial pulsations show changes compatible with right to left and left to right shunts.

HEMATOLOGIC RESPONSE IN HYPOPLASTIC ANEMIA DURING CORTISONE THERAPY, *W. L. Wilson,* J. F. Gamble* and R. A. Hettig*, Department of Medicine, Baylor University College of Medicine, and the Veterans Administration Hospital, Houston, Tex.

Because of various reports that cortisone may stimulate the bone marrow five cases of idiopathic hypoplastic anemia were treated with cortisone. Two patients showed no response, one showed a transitory rise in hemoglobin and neutrophils, another showed only a transitory rise in neutrophils, but the fifth case had an early marked rise in the total leukocyte count, later followed by a rise in the platelet count and the percentage of reticulocytes. When cortisone was discontinued, there was a return to control levels of these blood elements. These results were reproduced in each of five courses of cortisone therapy.

During the initial forty-eight hour period of the second course of cortisone therapy, total leukocyte and Arneth counts were done at frequent intervals and it was determined that the increase in the leukocytes was due almost entirely to an increase of the one- and two-lobed neutrophils. Serial bone marrow aspirations were also done on this patient and after the first course of cortisone an apparent increased cellularity of the aspirated marrow developed and persisted. This suggested that the rise in the neutrophil count was due to the formation and release of new cells.

OBSERVATIONS ON AN EXTRACT POSSESSING POTENT PROTEOLYTIC ACTIVITY DERIVED FROM PSEUDOMONAS AERUGINOSA. *Ellard M. Yow and Edna S. Townsend,** Department of Medicine, Baylor University College of Medicine, and the Ben Taub Infectious Disease Laboratory, Jefferson Davis Hospital, Houston, Tex.

It has been observed clinically that if a third degree burn or open wound is contaminated with Pseudomonas aeruginosa the damaged tissues are sometimes replaced by healthy granulation. At the same time attempts to apply skin grafts in the presence of this infection are frequently unsuccessful. These observations led to investigation of the proteolytic properties of various strains of P. aeruginosa.

A number of strains of pseudomonas were studied and revealed that a filtrate of a broth culture of all the strains possessed the ability to liquefy gelatin. A crude extract from one strain, isolated from an infant with gangrene of the skin due to pseudomonas, possessed proteolytic activity in dilutions up to 1:10,000. It was found to lyse blood clots, plasma clots, coagulated serum and coagulated human skin and muscle. Stability to changes in temperature and pH was observed and the active proteolytic substance could be consistently produced when the organism was subcultured in artificial media, the maximal titer being reached at about five days.

This substance has possible application to the débridement of thermal and physical injuries in living animals.

Case Reports

Chronic Keratoderma Blenorrhagica with Ankylosing Polyarthritis Deformans*

Report of a Case with Autopsy Findings

S. P. STUBBS, M.D., W. C. CORWIN, M.D. *and* E. B. HANAN, M.D.

Fayetteville, Arkansas *Springfield, Missouri*

KERATODERMA blenorrhagica is known principally to dermatologists. The case under consideration is reported because it is believed that internists should be reminded once more of the occasional occurrence of this disease and that they should be fully cognizant of its seriousness.

Keratoderma blenorrhagica was first described by Vidal in 1893.[1] Ladany and Hughes[2] gave the most comprehensive review of the subject and, as of 1946, were able to collect 166 cases reported in the literature. Since that time, with increased awareness of the disease, there have been many more reports. The question as to its etiology is not absolutely settled but most indications are that the disease is gonorrheal in origin. If the gonococcus is accepted as the etiologic agent, the incidence of keratoderma blenorrhagica is said to be one per 5,000 to 7,500 cases of gonorrhea.[3–5] As is the case with Reiter's disease, women demonstrate an unexplained comparative immunity, the ratio in keratoderma being about 15 men to one woman.[2] Individuals in their twenties and thirties are most susceptible.[2,6] In recent years penicillin has received much favor as a therapeutic agent in this disease but reports of several observers indicate that results are variable.[2,6–11]

CASE REPORT

The subject of this report was a well developed, well nourished twenty-four year old white man, who was admitted to the Fayetteville Veterans Hospital in November, 1947, with the chief complaint of "swelling and painful right knee and left ankle." He gave a history of developing a urethral discharge approximately five weeks prior to admission, following sexual exposure. He went to his local physician who treated him for uncomplicated gonorrheal urethritis. He received 200,000 units of aqueous penicillin in divided doses. Following this the discharge did not subside completely, and four or five days later he felt migratory joint pains. His physician administered sulfathiazole for three days plus an additional million units of penicillin. Approximately one month after the onset of pain the patient was admitted to the hospital.

Examination on admission revealed an ambulatory, young adult male. The left ankle was slightly swollen and tender on manipulation, and there was localized fever. The right knee was similarly swollen but to a more marked degree. There was no fluctuation. A thin, whitish, urethral discharge was noted which microscopically revealed a few pus cells but no bacteria. Between the date of admission in November, 1947, until transfer to Wadsworth, Kansas, V. A. Hospital in December, 1948, he had repeated courses of sulfadiazine, penicillin, streptomycin, dihydrostreptomycin, aureomycin and BAL without effect. In fact his joints showed increasing involvement, necessitating confinement to a wheel chair and finally to bed. His temperature ran from 101 to 103°F. and the sedimentation rate remained around 35 to 40 mm. per hour. Daily diathermy to various joints did not improve the situation.

In mid-December, 1947, some excoriation and desquamation of the plantar surfaces of the feet were noted. The skin lesions gradually progressed so that they ultimately affected the

* From the Medical Service, Veterans Administration Hospital, Fayetteville, Ark. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

feet as a whole, and concomitant involvement of the hands was noted. There was considerable desquamation of the superficial layers and loss of the nails of the fingers and toes. A papilliform transformation of the deeper layers of the skin was noted; and the pain and swelling of the wrists, shoulders and elbows progressed. In February, 1948, the patient complained of considerable pain of all major joints and definite papilliform keratotic skin lesions were seen on the plantar surfaces of the feet and the palmar surfaces of the hands, as well as along the lateral aspect of the legs and thighs. A purulent, foul-smelling discharge could be expressed from these areas. There was a lesser keratotic reaction involving the remainder of the surface of the body, including the scalp. By this time various wet compresses and ointments, including antihistaminics, had been applied locally; but they failed to heal the cutaneous lesions. In March, 1948, deformity of all the major and minor joints of the extremities was noted, particularly of the knees, which were becoming slightly abducted. The patient was given Hubbard tank baths daily; and due to the severity of the joint pains it required from that time on four attendants to lift the patient on and off the cart to take him to the Physiotherapy Department.

During this period of hospitalization in Fayetteville he was seen by several visiting dermatologists, who diagnosed his case variously as psoriatic arthropathy, gonorrheal blenorrhagica and keratoderma blenorrhagica. In December, 1948, the patient was transferred to the Veterans Hospital at Wadsworth, Kansas, where he would be under the continuous guidance of dermatologists who were not constantly available in Fayetteville. There various antibiotics, ointments and other local medications were employed, as suggested by visiting consultants, in an attempt to improve the patient's condition. Improvement was not attained. The patient also received massive doses of vitamins A and D. Cultures of the skin and blood for fungi were made and reported as negative. He was then taken to Kansas City for presentation to the Kansas City-St. Louis Dermatological Conference, where many dermatologists reviewed his case and offered their suggestions as to therapy. As a result, in May, 1949, fever therapy was begun, the patient being placed in a heat cabinet at 105°F. for one to three hours every other day, as his condition would permit. He did not tolerate this because of weakness and lassitude, and after five treatments it was discontinued.

As the patient's condition became worse, in January, 1950, he was transferred back to Fayetteville. Here examination revealed the patient was more emaciated and that he had apparently progressively gone downhill, since last examined a year previously. He was extremely crippled and deformed and complained of considerable pain in his joints. Due to ankylosis of the elbows he was unable to feed himself. The legs were held in a position of 90 degrees abduction, and 90 degrees flexion at the knees, with external rotation in relation to the thighs. There was ankylosis of the knees and ankylosis and enlargement of the interphalangeal joints. The nails were loose from the beds. There were heavy crusted areas on the ankles, the lower third of the legs, the lateral aspects of the thighs and, to a lesser degree, on the arms, face, abdomen and chest. The involved areas of the legs and thighs were considerably thickened with papilliform projections and with granulation tissue surrounded by purulent, crusted material. The patient required ever increasing amounts of codeine and pantapon for relief of pain. His appetite remained fairly good. He was afebrile but continued to have an elevated sedimentation rate, still averaging 35 mm. per hour. X-rays of the major joints now revealed generalized demineralization of moderate severity.

He began having episodes of projectile vomiting in April, 1950, from which he would rally without any residuals. On August 1, 1950, he complained of more severe pain and required narcotics more frequently. He then became stuporous and could be aroused only with some difficulty. Later he could not be aroused at all, although narcotics were withheld. On some days he was mentally clear and on others practically comatose. He became irrational on August 15th and hallucinated. Nine days later he went into a deep coma and expired.

NECROPSY FINDINGS

The severe malnutrition, emaciation and marked deformity as noted clinically were of course quite manifest. It was found that all the large joints of the upper and lower extremities and many of the small joints were ankylosed. The keratotic areas of the skin were of especial interest in that they revealed many papilliform projections surrounded by thick, yellowish exudate when scraped with the blunt edge of a

knife. This finding was most marked on the thighs, legs, ankles and feet. There was advanced desquamation of the skin of the face, neck, upper extremities and trunk. The skin of the legs was for all practical purposes necrotic. Great sloughs were easily removed with a blunt instrument, revealing underlying muscle, tendons and bone. Sloughing was also noted in oval areas of greenish discoloration on the dorsum of the feet. There was far advanced atrophy of the voluntary muscles, heart, adrenals, gastrointestinal tract, bladder, prostate and seminal vesicles.

The histologic features,[12–15] were considered to be compatible with the clinical diagnosis of chronic keratoderma blenorrhagica. The skin revealed severe hyperkeratosis and papillomatosis. The rete pegs were atrophic. The papillae were thin, and the capillaries were dilated and lined with prominent endothelium. There were moderate perivascular infiltrations of lymphoid and plasma cells, especially about the dilated capillaries. The hair follicles and the sebaceous and sudoriferous glands were atrophic.

SUMMARY

1. Keratoderma blenorrhagica, a rare disease, is briefly described.

2. A case, with necropsy findings, of an individual who survived this disorder for nearly three years despite devastating pain, repugnant disfiguration, extreme deformity and emaciation, is reported.

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Thyroid Carcinoma*

Visualization of a Distant Osseous Metastasis by Scintiscanner; Observations during I-131 Therapy

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RADIOACTIVE iodine has made possible an accurate and simple outline of the frontal profile of the human thyroid gland in a variety of abnormal functional and morphologic states.[1,2]

We are reporting a case in which a distant osseous metastasis from thyroid cancer was visualized *in vivo*. Serial observations were made in the course of I-131 therapy.

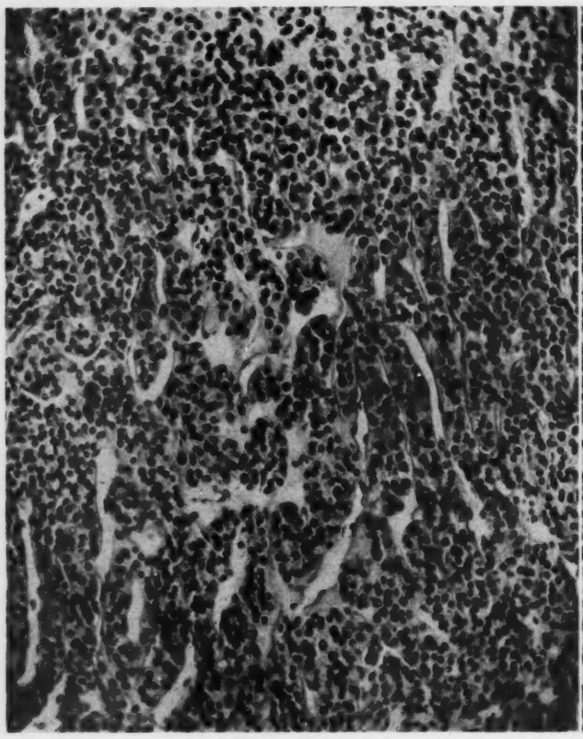

FIG. 1. Biopsy of osseous metastasis; × 180.

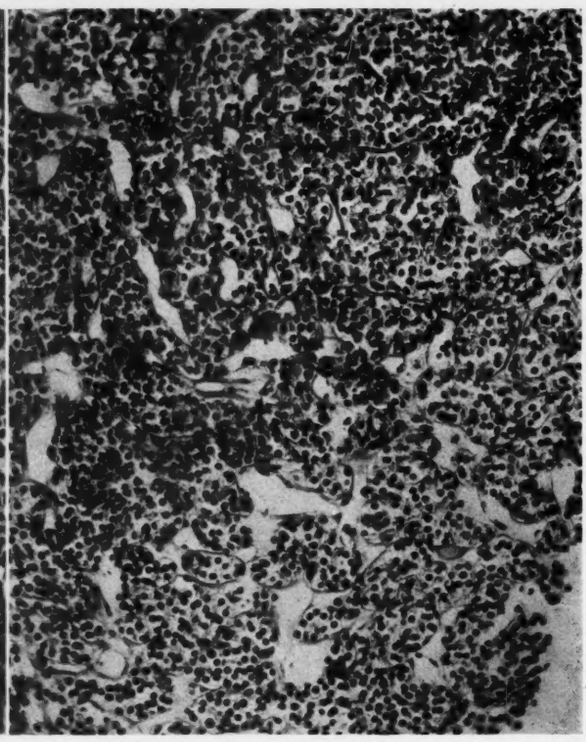

FIG. 2. Primary carcinoma of the thyroid gland; × 180.

CASE REPORT

Mrs. D. W., a fifty year old white woman, gave a history of gradual onset of poorly localized pain in the lumbar area radiating to the right hip and knee. The pain had become so severe that hospitalization was necessary. During the previous two months she had lost about 40 pounds in weight and had developed emotional instability and personality changes. X-ray study revealed a destructive lesion of the right transverse process and the pedicle of the third lumbar vertebra and partial erosion of the right transverse process of the second lumbar vertebra. Surgical exploration of the spine lesion on December 12, 1950, revealed extensive tumor tissue throughout the back muscles, arising from

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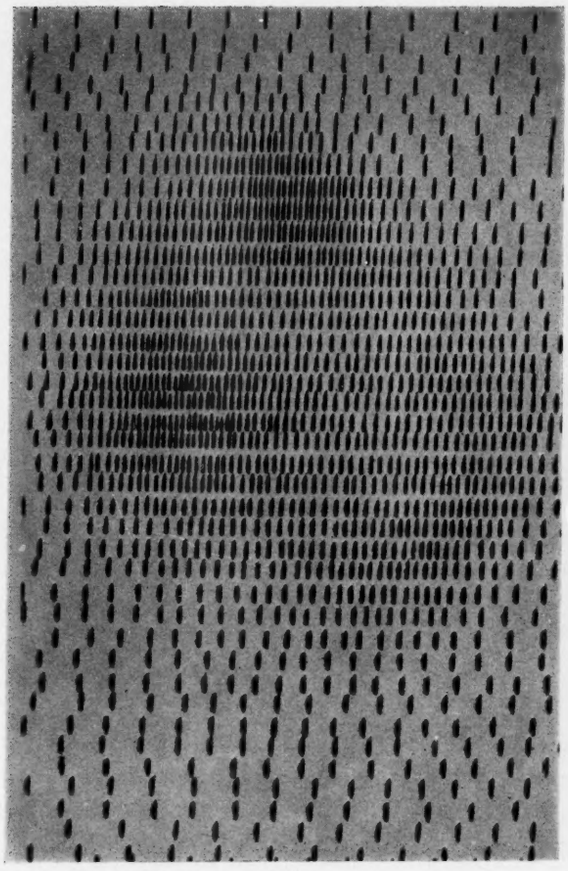

FIG. 3. Scintigram of the osseous metastasis.

FIG. 4. Postmortem photograph of sagittal section through metastatic tumor.

a defect of the right lamina of the third lumbar vertebra. The tumor tissue was very vascular and only a small portion could be removed. Microscopic study revealed adenocarcinoma of thyroid origin. (Fig. 1.) Ten days following surgery she was referred to one of us (N. W. S.) as a candidate for radioactive iodine therapy.

Examination of her neck revealed a 2 cm. firm, non-tender solitary nodule in the right lobe of the thyroid. Serum protein bound iodine was 5.2 μg./100 cc. The twenty-four-hour thyroid uptake was 26 per cent. After a tracer dose of 350 microcuries of radioiodine no activity could be demonstrated over the area of metastatic tumor. X-rays of the skull and chest showed no metastatic lesions.

Because of the failure of the secondary tumor to take up iodine the patient was referred to her private physician with the advice that total thyroidectomy be done and a course of roentgen therapy to the back be administered.

Mrs. D. W. was next seen February 13, 1951, seven weeks following a total thyroidectomy. She had failed to improve following roentgen therapy to her back. Microscopic examination of the thyroid nodule had confirmed the diagnosis of adenocarcinoma. (Fig. 2.) Following a tracer dose of 330 microcuries of I-131 there was no appreciable uptake over the thyroid gland. There was, however, a well localized area of activity centered approximately 2 cm. above the iliac crest and 5 cm. to the right of the midline. Serum protein bound iodine was 3.3 μg./100 cc. Therapy was begun at this time with 20 millicuries of I-131. External counting one, two and six days following this dose revealed an elliptical shaped 6 by 8 cm. area of activity just to the right of the third lumbar vertebra. Activity decreased at a rate corresponding to an effective half-life of 2.3 days. The twenty-four-hour uptake by the tumor was estimated as 18 per cent of the administered therapeutic dose of I-131.

During the next seven months the patient received an additional 218 millicuries of I-131 in six doses. Her physical condition gradually improved so that instead of being bedfast she

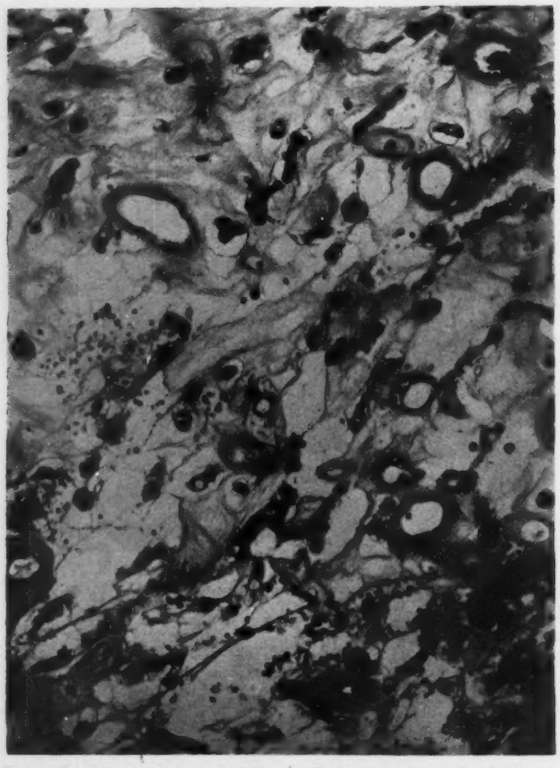

FIG. 5. Postmortem section of the metastatic lesion; × 200.

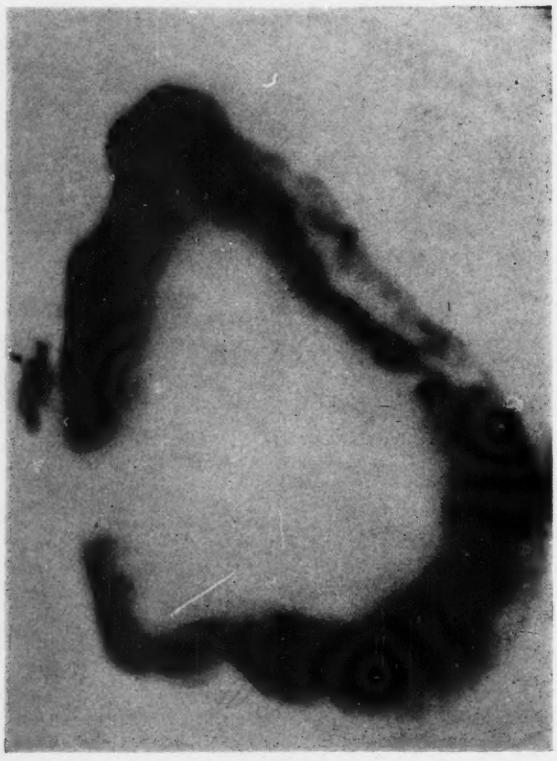

FIG. 6. Radioautograph of metastatic tumor; note activity in the periphery of the tumor.

was able to walk with the support of a back brace.

At no time did she develop clinical evidence of hypothyroidism. Serum protein bound iodine was 4.8 μg./100 cc. on May 10, 1951. Following her last dose of 44 millicuries of I-131 on November 13, 1951, the metastatic tumor was outlined by means of a gamma detecting directional scintillation counter (scintiscanner) then available only at the Veterans Administration Center. Serial scintigrams from two to twenty-one days after the therapeutic dose of I-131 showed no appreciable change in the size of the lesion. One of the scintigrams is shown. (Fig. 3.)

About three and one-half months following the last dose of I-131 and approximately ten months after the first therapeutic dose the patient became mentally depressed because of domestic difficulties and died following self-inflicted gunshot wounds of the chest and skull.

Autopsy revealed a well developed and well nourished woman. External examination revealed nothing of significance except for bullet wounds of the head and chest. Examination of the skull and brain revealed no secondary tumor. No thyroid tissue was found in the neck. Cervical lymph nodes were not enlarged. The left lung was collapsed. A bullet sinus tract extended through the base of the left lung. No tumor was found in the lung or chest cage. No other significant abnormality was found except for the 7 by 6.5 by 6 cm. tumor mass located posteriorly and to the right of the second and third lumbar vertebrae. The tumor was irregular in shape and had extended anteriorly to involve the second and third vertebral bodies. The vertebral processes were destroyed except for a few remnants on the left. The tumor appeared hemorrhagic and contained colloid filled spaces. (Fig. 4.) Microscopic examination of the tumor (Fig. 5) revealed small groups of tumor cells scattered in a large amount of pale pink-staining matrix, demonstrating profound changes compared with the biopsy specimen. (Fig. 1.) Radioautograph of a section through the osseous metastasis is shown in Figure 6. Analysis of the tumor for iodine revealed a concentration of 223 μg./100 gm. (The iodine content of normal thyroid is approximately 8,000 μg./100 gm.)

COMMENTS

This case has several features of interest. It verifies the observation that metastases from

carcinoma of the thyroid which previously did not accumulate radioactive iodine can do so after the primary carcinoma and the thyroid gland have been removed. Dobyns and Maloof[3] suggest that those patients who are most effectively treated with radioactive iodine possess tumors which initially take up some of the isotope and show a prompt increase after thyroidectomy. This was not demonstrated in our patient. However, since the histologic section from the metastasis revealed colloid, it is likely that some I-131 was accumulated by the metastasis in small amounts but not enough to be determined by external counting.

Of a series of thirty-five patients with carcinoma of the thyroid whose thyroid glands had been totally removed, twenty-one developed a significant increase in function of the metastatic lesions. Only two of these twenty-one patients showed enough increased avidity for I-131 to justify administration of I-131 in therapeutic amounts.[4] The increase of avidity for I-131 was demonstrated in our patient; and although 18 per cent uptake of the administered dose would not appear to be very high, it is at least five times higher than before thyroidectomy, the criterion used by Rall.[5] The clinical course, the histologic appearance of the tumor as seen at autopsy (Fig. 6) and the absence of toxic reactions (depression of the hemopoietic system, etc.) all suggest that I-131 therapy was of definite benefit.

It is reasonable to assume that the metastasis had begun to function after thyroidectomy and therefore treatment with I-131 was indicated. This is suggested by (1) absence of clinical evidence of hypothyroidism, (2) maintenance of the serum protein bound iodine level within normal range and (3) demonstration of I-131 accumulation by the metastasis.

The serial scintigrams of the metastasis confirmed Dobyns' and Maloof's[3] observation that there is little if any decrease in the size of the lesion after therapy with I-131.

The scintiscanner was found to delineate the lesion with accuracy. Extensive search for other metastases was made but none was found before or after death.

SUMMARY

A case of adenocarcinoma of the thyroid with a large solitary metastasis to the spine is presented. The metastasis was found not to accumulate I-131 but following surgical ablation of the primary tumor and the normal thyroid gland, the metastasis began to accumulate I-131 in significant amounts (18 per cent of an orally administered dose).

The metastasis was demonstrated visually by means of a gamma detecting scintiscanner and its progress during a course of I-131 therapy was followed by repeated scintigrams.

The interesting features of the case are discussed.

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Traumatic Chylothorax*

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Injury of the thoracic duct in the chest and ensuing escape of chyle into the free pleural cavity constitutes a grave catastrophe, about 50 per cent of the cases hitherto reported having proved fatal.[8] Traumatic chylothorax is uncommon; according to Mead,[2] fifty-eight cases have been reported up to 1946, when Lampson[5] reported a case in which recovery was obtained by ligation of the thoracic duct in the lower chest.

The purpose of this paper is to present a case of traumatic chylothorax with recovery following repeated thoracenteses and the use of enzymatic dèbridement and lipophilic coal dye (D and C Green No. 6)† as a method of diagnosis.

The thoracic duct is a thin structure and constitutes the main collecting vessel of the lymphatic system. It begins in the epigastric region at the height of the first and second lumbar vertebrae as an elongated dilatation, "the cisterna chyli," into which the right and left lumbar lymphatic trunks empty. From the cistern the duct runs upward along the right side of the aorta, traversing the aortic hiatus. It crosses the median plane from right to left and ascends to the root of the neck where it empties into the left innominate vein. The duct is provided with valves, the most important of which are at its termination to prevent the passing of blood into the duct. Lee has shown that there are many collateral branches communicating the main trunk to the lumbar, azygos and intercostal veins. Changes in the intrathoracic pressure, as well as the accumulation of the chyle in the cisterna chyli, are important factors in propulsion of the chyle upward along the duct. It has been estimated that the flow of chyle is approximately 2,000 cc. per day.

The chyle is a thin, milky fluid with a specific gravity of 1.010 to 1.020 and alkaline reaction. It contains lipoid substances which are stained by Sudan 111 or similar coal tar dye. The composition of chyle is approximately the same as serum, with some variations according to the diet. The chyle is bacteriostatic. This property has been repeatedly demonstrated by different authors.

The thoracic duct is normally surrounded by loose connective tissue and thus is freely movable and elastic. This may be the reason why its rupture following trauma does not occur more frequently. However, fixation of the duct to the surface of the vertebrae by inflammatory process, congenital band, malignant infiltration or the state of distention of the duct may contribute to its vulnerability. Once the thoracic duct is ruptured the chyle escapes into the mediastinum and, during an interval which varies from a few days to as long as one month, it gradually infiltrates the pleural cavity and compresses the lung so as to produce respiratory embarrassment. The local effect of chyle upon the pleural surface is important since the chemical inflammatory process thus produced will result in thickening of the pleura by an exudative and fibrinous layer over the visceral pleura with formation of a "peel" and collapse and compression of the lung.[1] In patients in whom this condition has been present for a long period of time necessitating repeated thoracenteses, hypoproteinemia, weight loss and inanition become very marked presumably because of diversion of essential products of nutrition from the circulation. Death from chylothorax, unless the condition is unrecognized and allowed to cause asphyxia, is due to progressive loss of fluid, protein and fat. Since the chyle is bacteriostatic, no instance in which infection causing death has been reported.

The diagnosis of traumatic chylothorax can usually be made without difficulty when there are signs and symptoms of pleural effusion following trauma and by aspiration of characteristic milky fluid from the pleura. The use of lipophilic dye as a method of diagnosis is a

† D and C Green No. 6 was supplied through the courtesy of National Aniline Division, Allied Chemical & Dye Corporation, New York 6, N. Y.

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valuable procedure. In 1930 Fletcher[7] gave Sudan III to a patient and, upon recovering the dye in urine, made the diagnosis of chylouria. Klepser[6] in 1949 reported the use of the same method for diagnosis of a case of traumatic chylothorax. The use of lipophilic dye is useful not only for diagnostic purposes but also is of great help in identifying the thoracic duct should occasion arise for ligation below the point of rupture.

The seriousness and the rarity of traumatic chylothorax have led to diverse opinion and speculations concerning management. Frequent thoracenteses, pneumothorax, instillation of substances producing fibrinous[3] reaction, intravenous injection of chyle,[4] phrenic crush, etc., have been used by different authors but with questionable success. Intrathoracic ligation of the ductus below the site of rupture was attempted by Lampson and Mead with a satisfactory result. However, considering all the factors involved in chylothorax and studying cases reported in the literature, it seems that the plan of management should be based on the following: first, replacement of protein lost in the chyle by intravenous administration of protein hydrolysates as well as a high protein diet; second, removal of the chyle from the pleural cavity to prevent collapse of the lung with pleural thickening and subsequent respiratory embarrassment; if reformation of the chyle is rapid and there seems to be no gradual decrease, intercostal drainage may be instituted; third, ligation of the thoracic ducts should be used only when these simpler methods of therapy have failed.

The case presented in this paper brings out the fact that if conservative measures seem to fail because of loculation of the chylothorax preventing satisfactory aspiration of the chyle, the use of streptokinase and streptodornase may overcome this complication.

CASE REPORT

W. H., No. 96694, a sixty-four year old obese man, was admitted to the Mountainside Hospital on May 14, 1952, with the chief complaint of shortness of breath. The present illness started two weeks prior to admission when he sustained a forced hyperextension of the spine in an auto accident. He was immediately brought to a hospital. Roentgenograms of the spine failed to reveal presence of any fracture. Three days later the patient started to experience a great deal of respiratory distress. Roentgenograms of the chest at this time revealed the presence of a considerable amount of fluid in the right pleural cavity. Thoracentesis was performed and 1,500 cc. of milky fluid were obtained. The patient's condition improved immediately. However, two days later the respiratory distress recurred. He was then transferred to Mountainside Hospital for further treatment.

The family history was non-contributory; personal history was essentially negative. He was a farmer and always enjoyed good health except for an appendectomy fifteen years previously.

Physical examination disclosed the following positive findings: weight, 200 pounds; temperature, 100°F.; pulse, 99; respiration, 20; blood pressure, 140/80. His appearance was that of an obese man in no acute distress but slightly cyanotic and complaining of a moderate amount of pain in the right chest. Systemic review was negative except for the presence of dullness in the right chest up to the fifth interspace and a slight cyanosis of the extremities.

Laboratory findings were as follows: urine, normal except for the presence of 30 to 50 white blood cells per high power field; red blood count, 5,290,000; white blood count, 6,700 with 72 per cent polymorphonuclears and 28 per cent lymphocytes; hematocrit, 51 per cent; sedimentation rate, 87 mm./hour westergren; blood chemistry: total protein, 5.6; albumin, 3.8; globulin, 1.8; chlorides, 112.5 mEq./L. serum; npn, 50 mg./100 cc. blood; cholesterol, 210 mg./100 cc. serum; cholesterol esters, 129 mg./100 cc. serum.

Roentgenogram of the chest at the time of admission revealed the presence of pleural effusion on the right side. Thoracentesis was performed and 1,500 cc. of milky fluid obtained. Following this procedure, the patient felt much more comfortable. Pathologic examination of the fluid revealed it to consist of chyle; bacteriologic studies were negative.

Repeated thoracenteses were performed daily and there seemed to be a gradual decrease in the amount of chyle obtainable by this method although roentgenograms of the chest failed to show any substantial change. On the sixth day of admission it was believed that the reason for our inability to withdraw the chyle from the pleural cavity was due to loculation of the fluid. At this time, 100,000 units of streptokinase and 40,000 units of streptodornase were instilled in

the pleural cavity. A few hours following this procedure, the patient felt quite uncomfortable and experienced a great deal of chest pain and difficulty in breathing. The temperature rose from normal to 101°F. A sedative, aspirin and oxygen were administered. However, the pain and respiratory distress became very acute nine hours after streptokinase therapy. At this time thoracentesis was performed and 1,000 cc. of chyle obtained. The patient felt much more comfortable and the temperature declined to within normal limits.

On the ninth hospital day a glassful of heavy cream dyed green with D and C No. 6 was given to the patient. Four hours later thoracentesis was performed and green chyle was obtained.

Treatment by high protein diet in conjunction with daily parenteral administration of protein hydrolysate and daily thoracentesis was continued and gradually the amount of chyle obtained was decreased until, on the fourteenth hospital day, the flow of chyle ceased entirely. The patient was kept under observation for another week and discharged, entirely symptom-free, on the twenty-first hospital day.

The patient has been followed for two months and seems to be entirely symptom-free. There has been a 10 pound gain in weight since discharge from the hospital. The last roentgenogram of the chest fails to show the presence of any pleural effusion.

SUMMARY AND CONCLUSION

A case of traumatic chylothorax, secondary to traumatic hyperextension of the spine, is presented.

The use of a lipophilic dye was found very valuable as a diagnostic aid and its value for outlining the duct, should surgery be contemplated, is discussed.

The patient responded satisfactorily to repeated thoracenteses and prevention of loculation of the pleural effusion by the use of enzymatic dèbridement.

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The American Journal of Medicine

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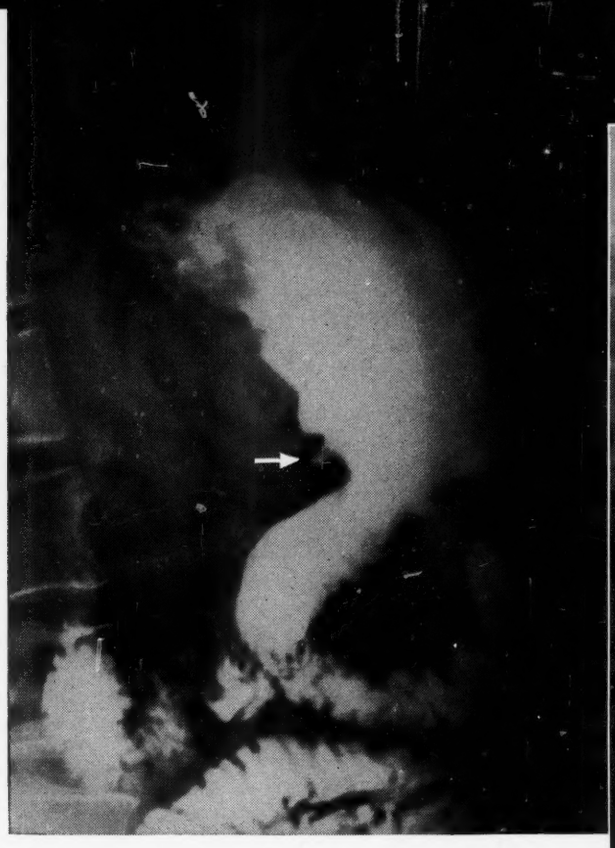
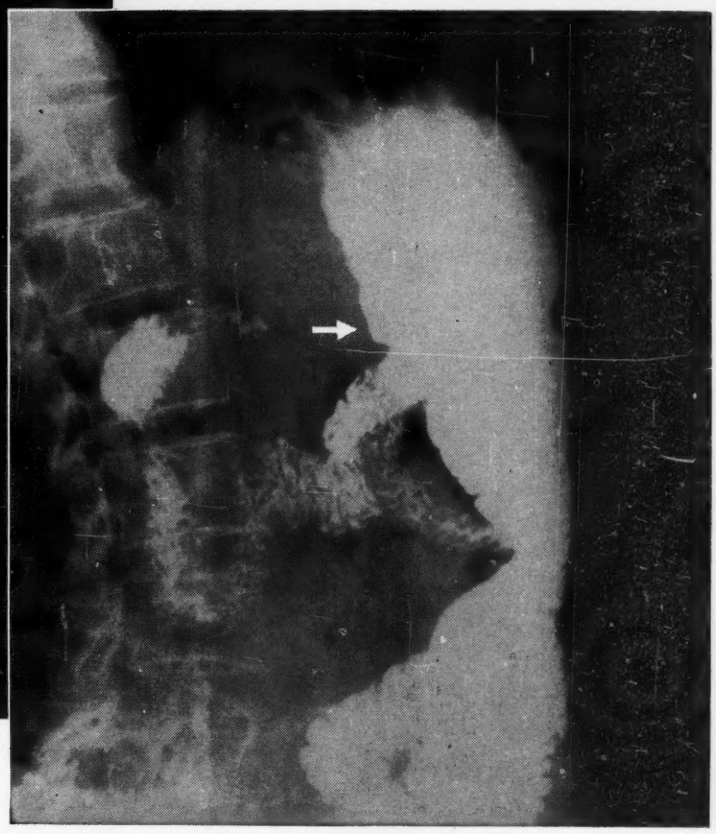


Fig. 1: "Roentgen examination . . . revealed the ulcer to be very much in evidence."

Fig. 2: In ten weeks "the ulcer niche was no longer in evidence roentgenologically or gastroscopically."



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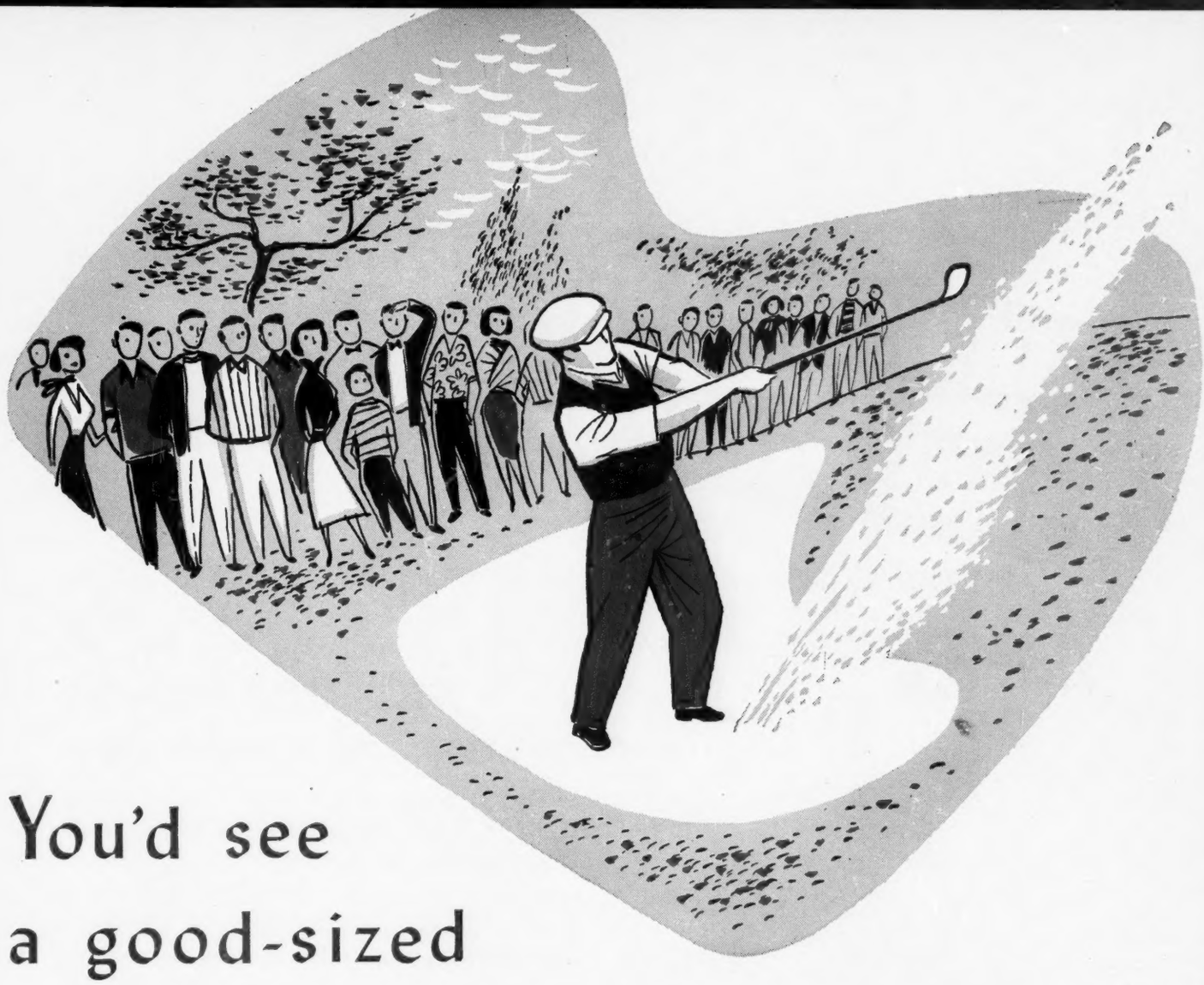

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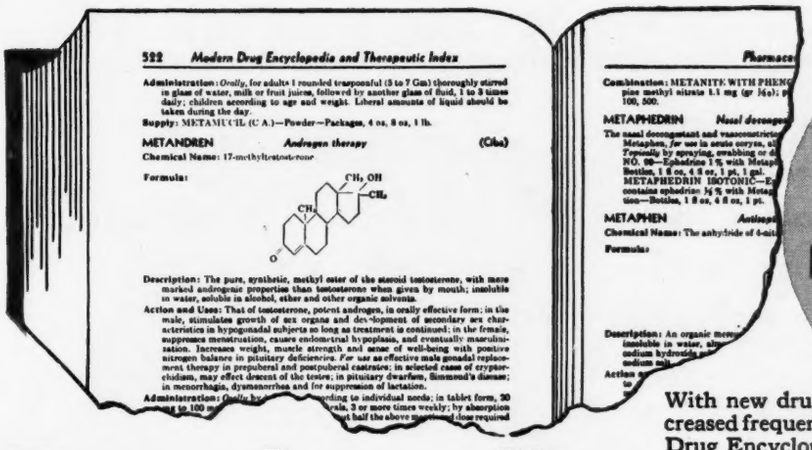
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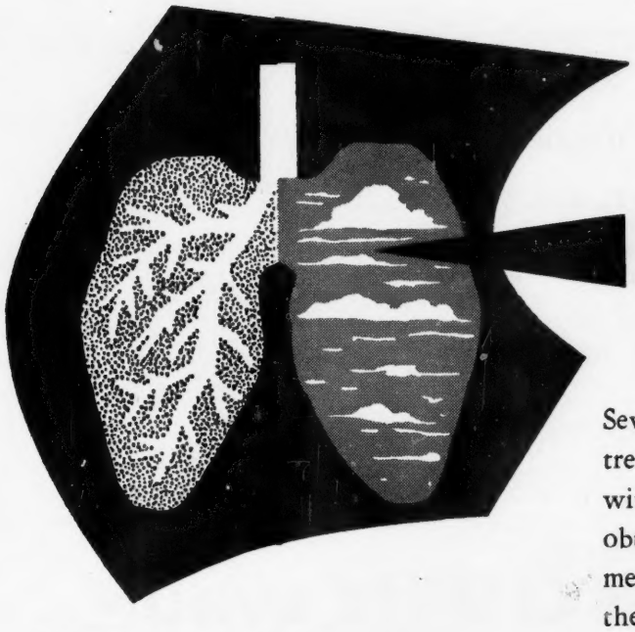

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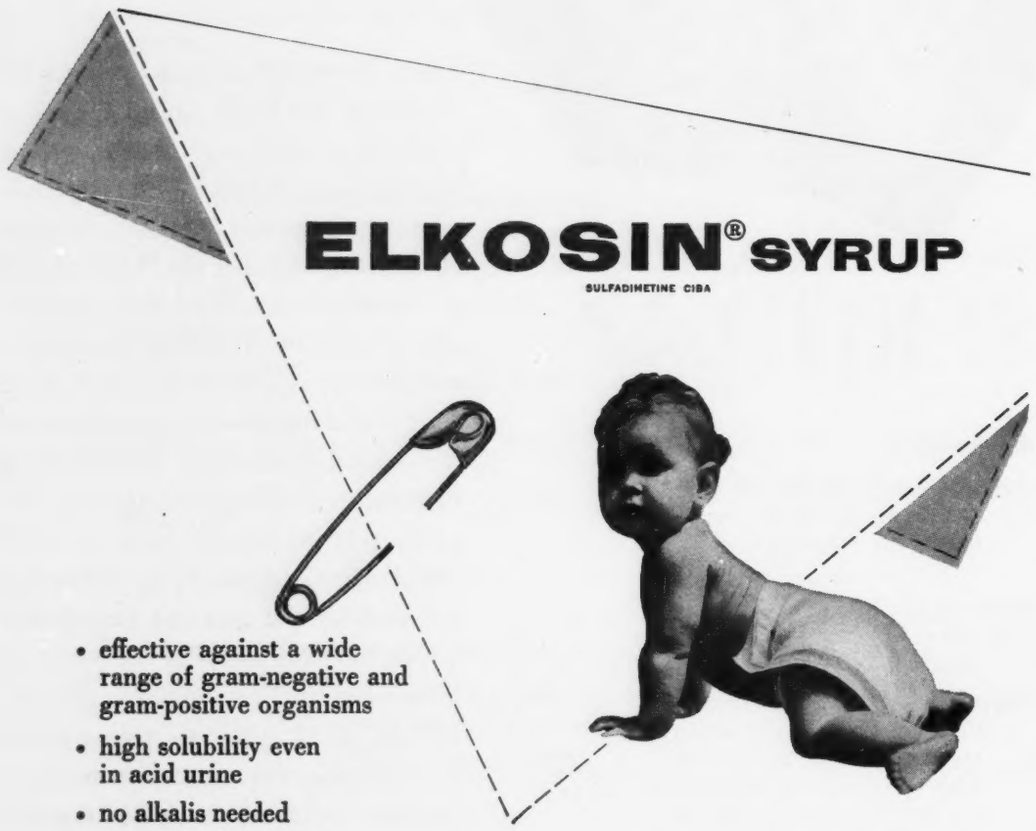
PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH

Ciba SUMMIT, N. J.

In the "diaper age"—
safer, simpler treatment
for urinary infections

ELKOSIN® SYRUP
SULFADIMETINE CIBA



- effective against a wide range of gram-negative and gram-positive organisms
- high solubility even in acid urine
- no alkalis needed
- finer particle size . . . for better suspension . . . uniform dosage
- mixes readily with milk, fruit juices

ELKOSIN SYRUP - a microcrystalline suspension of sulfadimetine in a strawberry-flavored syrup — 0.25 Gm. per teaspoonful (4 cc.). Pints. Also 0.5 Gm. double-scored tablets. Bottles of 100 and 1000.

ELKOSIN *a new advance in sulfonamide safety*

2/1893M

Waterproof Protection
AGAINST CONTACT DERMATITIS

. . . new plasticized cream resists washing, lasts longer

INDICATIONS: Protection of skin from *industrial dermatoses,* such as sensitivity to chemicals, paints, dyes and cutting oils; *household skin allergies,* such as soap and water dermatitis and sensitivity to cosmetics, clothing dyes, solvents, cleaning and polishing agents; *professional allergies* to procaine, penicillin, detergents and various laboratory solutions; *post-surgical reactions* to excoriating body fluids; and *irritation by scratching* of dry eczematous or neurodermatitic lesions.

CONTRAINDICATIONS: None except premature application on wet, exudative lesions.

APPLICATION: Twice daily for 10 days to two weeks to build up protective layer. Continued protection can then be maintained with a single application every one or two days. Massage into skin gently and over entire area; avoid actual rubbing in any one region; smooth in until no longer visible. When used on hands, apply also under fingernails.

HOW SUPPLIED: By pharmacies in one-ounce tubes with slip-off labels; also in one-pound jars.

No NEED for six or eight different skin creams to suit individual conditions — with COVICONE Cream, a single product provides protection against a wide variety of sensitizing agents from corrosive industrial materials to common household allergens. Resisting removal by ordinary washing, COVICONE is especially useful where prolonged or continuous protection is desired, as in cases of occupational nature. Invisible, plastic-like coating maintained with infrequent applications. In vanishing cream base, COVICONE is not sticky or greasy. Abbott

COVICONE
REG. U.S. PAT. OFF.
CREAM

(Abbott's Protective Skin Cream)

1-172

an improved approach to ideal hypotensive therapy

Low toxicity. The only hypotensive drug that causes no dangerous reactions, and almost no unpleasant ones.

Slow, smooth action. The hypotensive effect is more stable than with other agents. Critical adjustment of dosage is unnecessary. Tolerance to the hypotensive effect has not been reported.

Well suited to patients with relatively mild, labile hypertension. A valuable adjunct to other agents in advanced hypertension.

Bradycardia and mild sedation increase its value in most cases. Symptomatic improvement is usually marked.

Convenient, safe to prescribe

The usual starting dose is 2 tablets twice daily. If blood pressure does not begin to fall in 7 to 14 days, and the medication is well tolerated, the dose may be safely increased. Should there be a complaint of excessive sleepiness, the dose should be reduced. Some patients are adequately maintained on as little as one tablet per day.

Dosage of other agents (veratrum or hydralazine) used in conjunction with Raudixin must be carefully adjusted to the response of the patient. If Raudixin is added to another maintenance regimen, the usual dose is applicable, and it is often possible to reduce the dose of the other agent or agents.

Supplied in tablets of 50 mg., bottles of 100 and 1000.

SQUIBB

RAUDIXIN
SQUIBB RAUWOLFIA SERPENTINA
Tablets

'RAUDIXIN' IS A TRADEMARK

Aminodrox

Aminodrox

Aminodrox

Aminodrox

Aminodrox

Aminodrox

Heard at the staff meeting . . .

increases the usefulness of oral aminophylline

send for detailed literature and sample

THE S. E. MASSENGILL CO.

BRISTOL, TENNESSEE

In the form of AMINODROX, three out of four patients can be given therapeutically effective *oral* doses of aminophylline.

This is possible with AMINODROX because gastric disturbance is avoided.

How congestive heart failure, bronchial and cardiac asthma, status asthmaticus and paroxysmal dyspnea can be treated successfully with *oral* aminophylline in the form of AMINODROX.

Aminodrox Tablets contain 1 1/2 gr. aminophylline with 2 gr. activated aluminum hydroxide.

Aminodrox-Forte Tablets contain 3 gr. aminophylline with 4 gr. activated aluminum hydroxide.

Also available with 1/4 gr. phenobarbital.

Q.S.

is now possible

FOR LARGE DOSAGE OF ASPIRIN...

THE FIRST CLINICALLY PROVEN ENTERIC-COATED ASPIRIN

ASTERIC Brewer

ASTERIC Brewer (5 gr. enteric-coated Aspirin) ***Allows Greater Dosages***— 40, 50, 60, 70 or more grains daily as required where gastric distress and other irritating symptoms resulting from high dosages of plain aspirin tablets are contraindicated.

ASTERIC Brewer is indicated in the treatment of certain rheumatic disorders requiring maximal dosage of aspirin over long periods. *"Enteric-coated aspirin (ASTERIC) has an analgesic effect equal to that of regular aspirin and the onset of its action is only slightly delayed."* Clinically it was shown that equal blood levels were obtained.*

ASTERIC Brewer (5 gr. enteric-coated Aspirin) will be found beneficial for those patients suffering from hemorrhagic gastritis resulting from the irritating effects of plain aspirin and for cases of peptic ulcer which require acetylsalicylic acid therapy.

ASTERIC Brewer (5 gr. enteric-coated marbleized tablets) supplied in bottles of 100 and 1000.

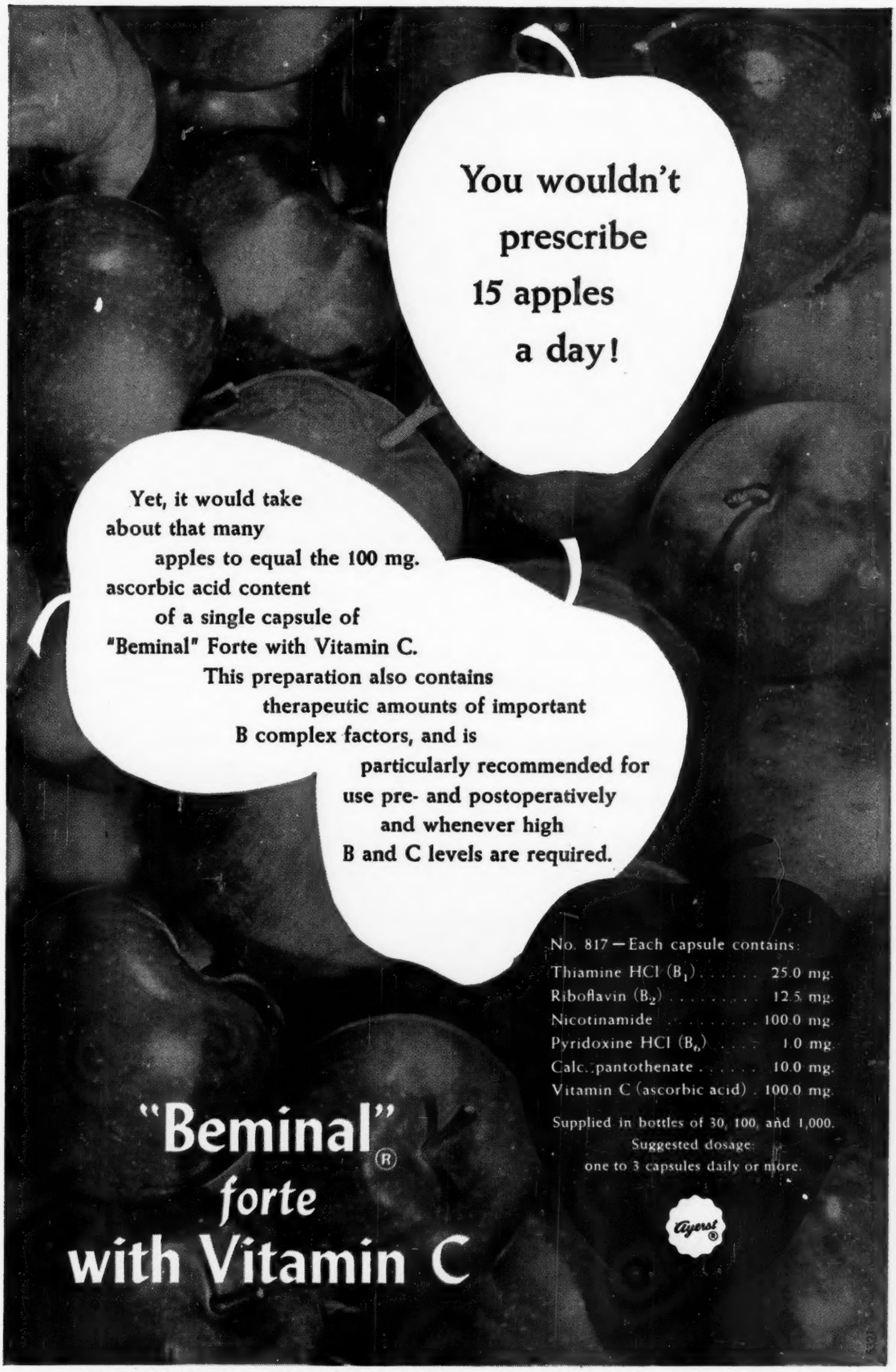
For samples—just send your ℞ blank marked—13AS6

*Talkov, R. H., Ropes, M. W., and Bauer, W.: *The Value of Enteric Coated Aspirin.* N.E.J. Med. 242,19 (Jan. 5) 1950.

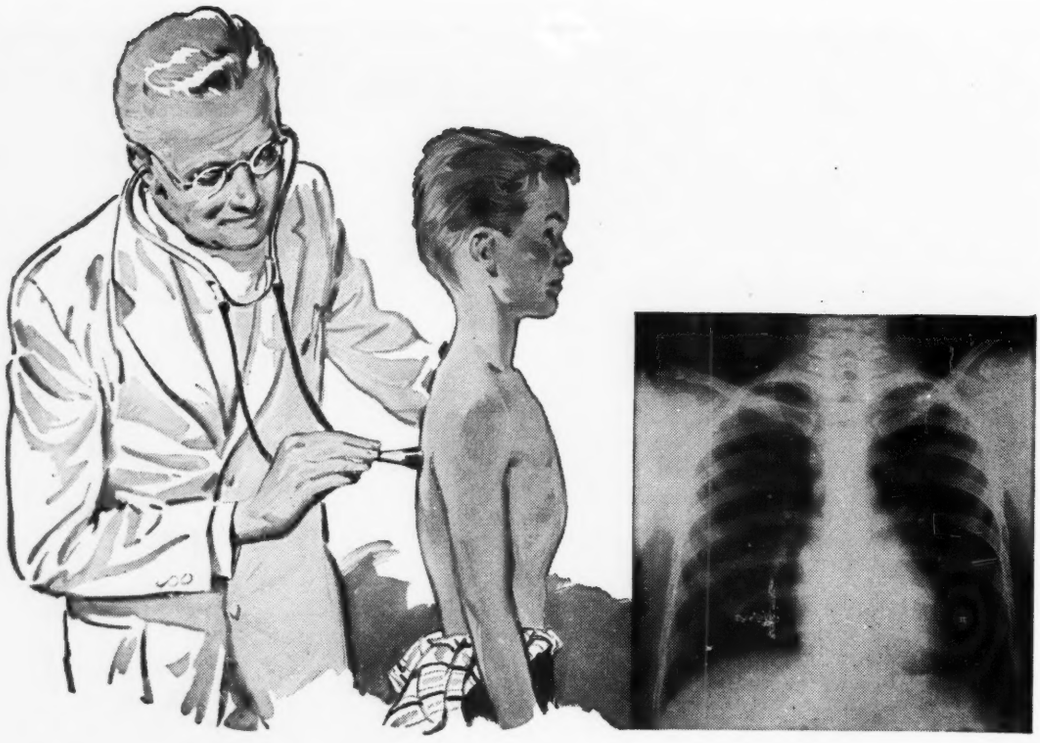
Brewer EST. 1852

BREWER & COMPANY, INC.

WORCESTER 8, MASSACHUSETTS U.S.A.


You wouldn't prescribe 15 apples a day!
Yet, it would take about that many apples to equal the 100 mg. ascorbic acid content of a single capsule of "Beminal" Forte with Vitamin C.
This preparation also contains therapeutic amounts of important B complex factors, and is particularly recommended for use pre- and postoperatively and whenever high B and C levels are required.
No. 817 — Each capsule contains:
Thiamine HCl (B_1) . . . . . 25.0 mg.
Riboflavin (B_2) . . . . . 12.5 mg.
Nicotinamide . . . . . 100.0 mg.
Pyridoxine HCl (B_6) . . . . 1.0 mg.
Calc. pantothenate . . . . . 10.0 mg.
Vitamin C (ascorbic acid) . 100.0 mg.
Supplied in bottles of 30, 100, and 1,000.
Suggested dosage:
one to 3 capsules daily or more.
"Beminal"®
forte
with Vitamin C
Ayerst®

AYERST, McKENNA & HARRISON LIMITED • New York, N. Y. • Montreal, Canada



A drug of choice in tuberculosis

As therapeutically active as streptomycin, CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK is less toxic to the vestibular apparatus, minimizes pain and swelling on injection, and may be used even in some patients allergic to streptomycin.

This preferred product is available in dry powder form and in convenient ready-to-inject form as SOLUTION OF CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK.

PARA-AMINOSALICYLIC ACID MERCK (PAS), when used in combination with CRYSTALLINE DIHYDROSTREPTOMYCIN SULFATE MERCK, prolongs the effective period of antibiotic therapy by inhibiting or delaying the development of bacterial resistance.

Crystalline Dihydrostreptomycin Sulfate Merck

COUNCIL ACCEPTED

Research and Production for the Nation's Health

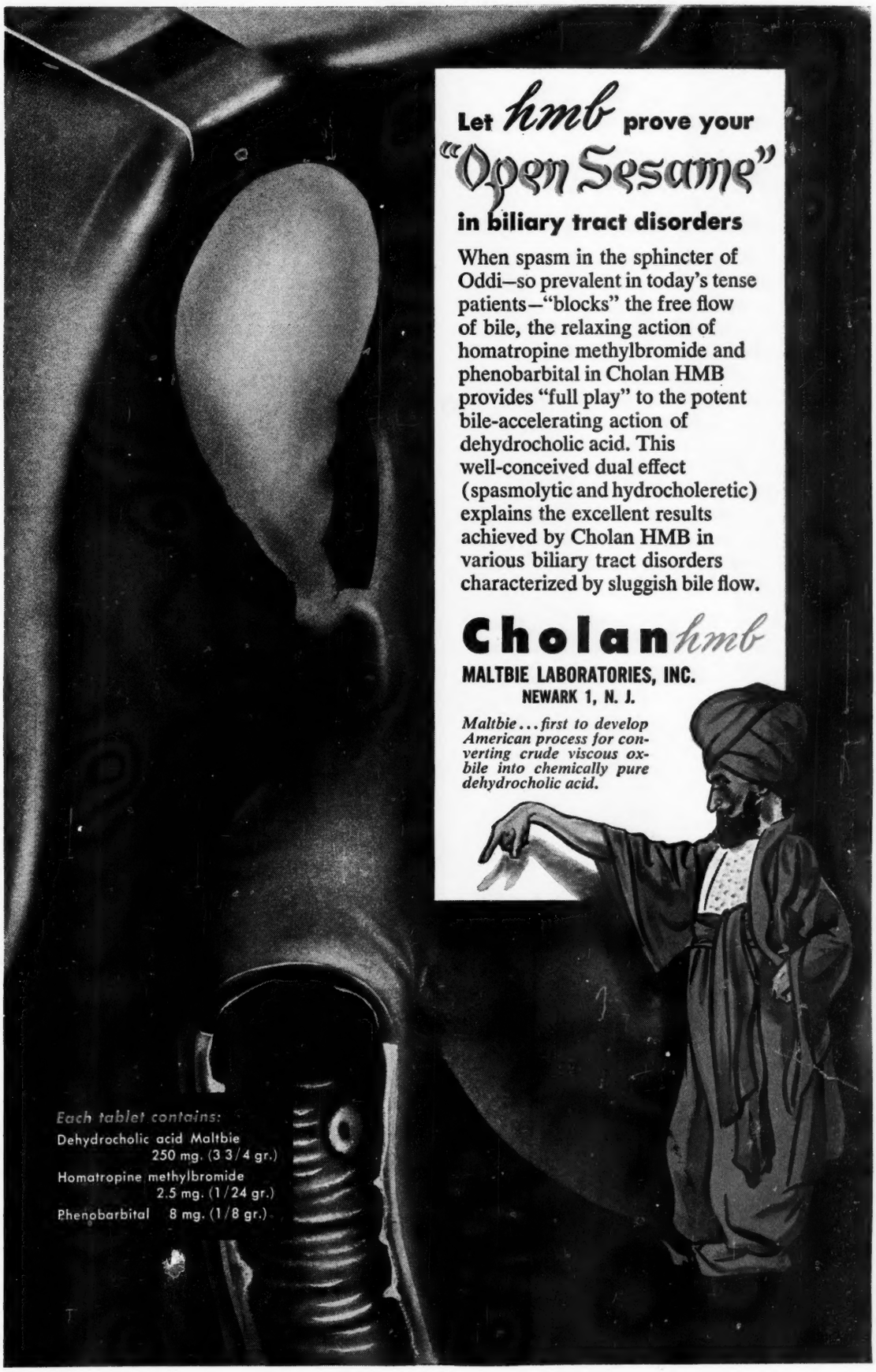
MERCK

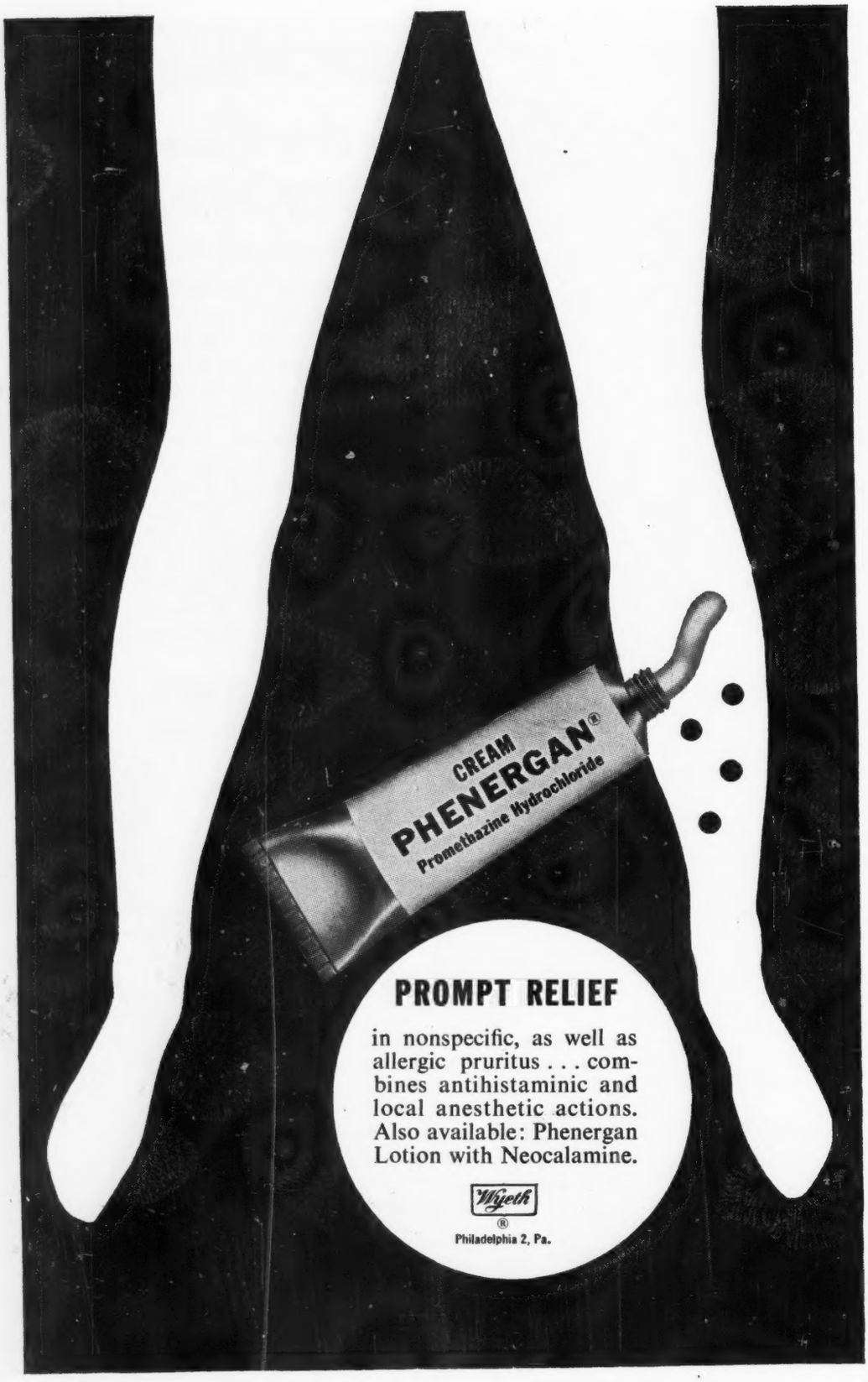
MERCK & CO., INC.

Manufacturing Chemists

RAHWAY, NEW JERSEY

In Canada: MERCK & CO. Limited—Montreal


Let hmb prove your
"Open Sesame"
in biliary tract disorders
When spasm in the sphincter of Oddi—so prevalent in today's tense patients—"blocks" the free flow of bile, the relaxing action of homatropine methylbromide and phenobarbital in Cholan HMB provides "full play" to the potent bile-accelerating action of dehydrocholic acid. This well-conceived dual effect (spasmolytic and hydrocholeretic) explains the excellent results achieved by Cholan HMB in various biliary tract disorders characterized by sluggish bile flow.
Cholan hmb
MALTBIE LABORATORIES, INC.
NEWARK 1, N. J.
Maltbie... first to develop American process for converting crude viscous ox-bile into chemically pure dehydrocholic acid.
Each tablet contains:
Dehydrocholic acid Maltbie 250 mg. (3 3/4 gr.)
Homatropine methylbromide 2.5 mg. (1/24 gr.)
Phenobarbital 8 mg. (1/8 gr.)


CREAM
PHENERGAN®
Promethazine Hydrochloride
PROMPT RELIEF
in nonspecific, as well as allergic pruritus . . . combines antihistaminic and local anesthetic actions. Also available: Phenergan Lotion with Neocalamine.
Wyeth®
Philadelphia 2, Pa.

unprecedented antimalarial action

'DARAPRIM' brand

Pyrimethamine

U. S. Patents No. 2,576,989 and No. 2,602.794

discovered and developed at

The Wellcome Research Laboratories

'DARAPRIM' is the first drug known to affect exoerythrocytic as well as erythrocytic forms of *P. vivax* at therapeutic dosage levels. There is also evidence that it sterilizes the gametocytes of *P. falciparum*.

The total advantage is threefold:

1. Potency in suppressive prophylaxis.

2. Improved transmission blockade.

3. Action on relapsing forms.

TASTELESS and virtually non-toxic, 'Daraprim' is so potent that only 25 mg. per week is required for suppressive prophylaxis, and one or two doses of 50 mg. for treatment.

'DARAPRIM' brand
Pyrimethamine, 25 mg.,
Compressed, scored

Boxes of 30 and
Bottles of 1000

Complete information will be sent on request.

BURROUGHS WELLCOME & CO. (U. S. A.) INC., TUCKAHOE 7, NEW YORK

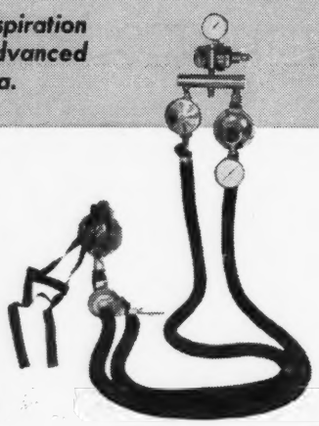
A complete line of modern equipment for

***ARTIFICIAL RESPIRATION** and*

INHALATIONAL THERAPY

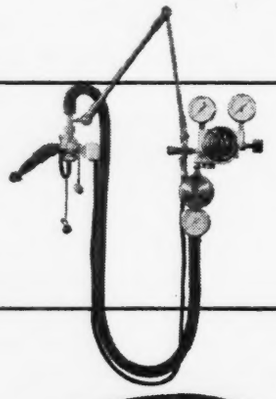
by M·S·A

Proved in service, the M.S.A. product line of artificial respiration and inhalational therapy equipment permits the most advanced techniques in treating the patient in either apnea or anoxia.



THE M·S·A DEMAND PNEOPHORE

This versatile instrument, combining automatic intermittent positive pressure, and flow without pressure when desired, is ideal for effective treatment in apnea and other respiratory emergencies. The Demand Pneophore has found wide acceptance in the treatment of pulmonary edema because of its mild, positive pressure which retards the entrance of fluid into the lungs and maintains oxygen saturation. A simple adjustment equips the instrument for oxygen administration without positive pressure. Ask for complete details.

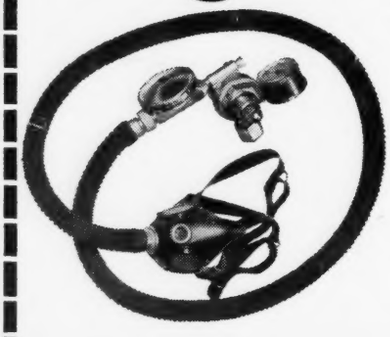


THE M·S·A PULMONARY VENTILATOR

An effective instrument for the application of aerosols such as broncho-dilators and bacterio-static agents under intermittent positive pressure assuring effective distribution of the drugs throughout the respiratory tract.

THE M·S·A OXYGEN THERAPY UNIT

This instrument supplies oxygen on inspiratory demand to patients with voluntary respiration. Fits any oxygen cylinder or piped system. Ideal device for oxygen administration in recovery rooms or elsewhere throughout the hospital.



M·S·A PNEOLATOR

Self-contained artificial respiration device that supplies oxygen under intermittent positive pressure to asphyxia victims, automatically, safely, without suction.

MSA
SAFETY EQUIPMENT HEADQUARTERS

MINE SAFETY APPLIANCES COMPANY
Braddock, Thomas & Meade Streets
Pittsburgh 8, Pa.
At Your Service: 82 Branch Offices
in the United States and Canada

for the "squeeze" of g.i. spasm

antispasmodic action virtually without atropinism . . .

through the selective spasmolysis of homatropine methylbromide (one-thirtieth as toxic as atropine) . . . *plus* the sedation of phenobarbital.

Each yellow tablet of MESOPIN-PB* or teaspoonful of yellow elixir contains 2.5 mg. homatropine methylbromide and 15 mg. phenobarbital. Also available as MESOPIN Plain (without phenobarbital) in white tablets, green elixir, and powder.

* Trademark of Endo Products Inc.

MESOPIN-PB

Trademark

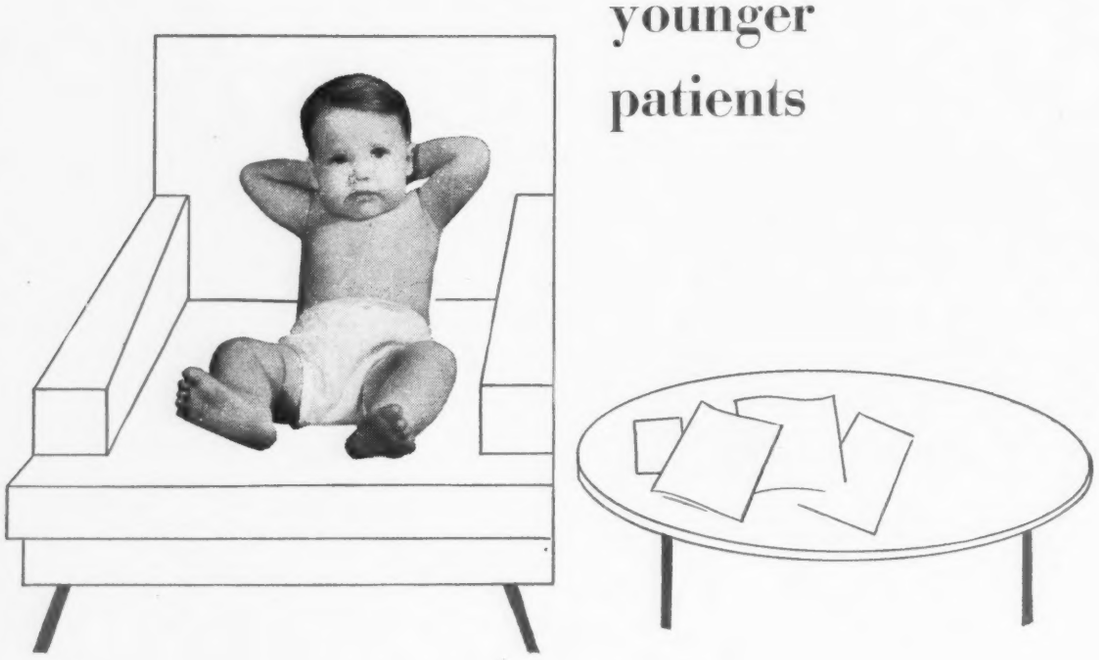
(Homatropine Methylbromide and Phenobarbital)

Endo®

Samples? Just write to:

Endo Products Inc., Richmond Hill 18, New York

New for your younger patients



CRYSTALLINE

Terramycin

BRAND OF OXYTETRACYCLINE • AMPHOTERIC

FOR WELL-TOLERATED, PROMPTLY EFFECTIVE BROAD-SPECTRUM THERAPY

PEDIATRIC DROPS

1.0 GRAM

new economy in drop dosage treatment

Each bottle of Terramycin Pediatric Drops supplies 1.0 gram of Terramycin, often a sufficient total dose for therapy of many common illnesses.

delicious raspberry flavor

The same good taste which makes Terramycin Oral Suspension a favorite for older children and adults on broad-spectrum therapy.

new flexibility in infant dosage schedules

Nonalcoholic Terramycin Pediatric Drops supplies 100 mg. of pure crystalline Terramycin amphoteric in each cc. to meet most infant dosage requirements; may be diluted as required.

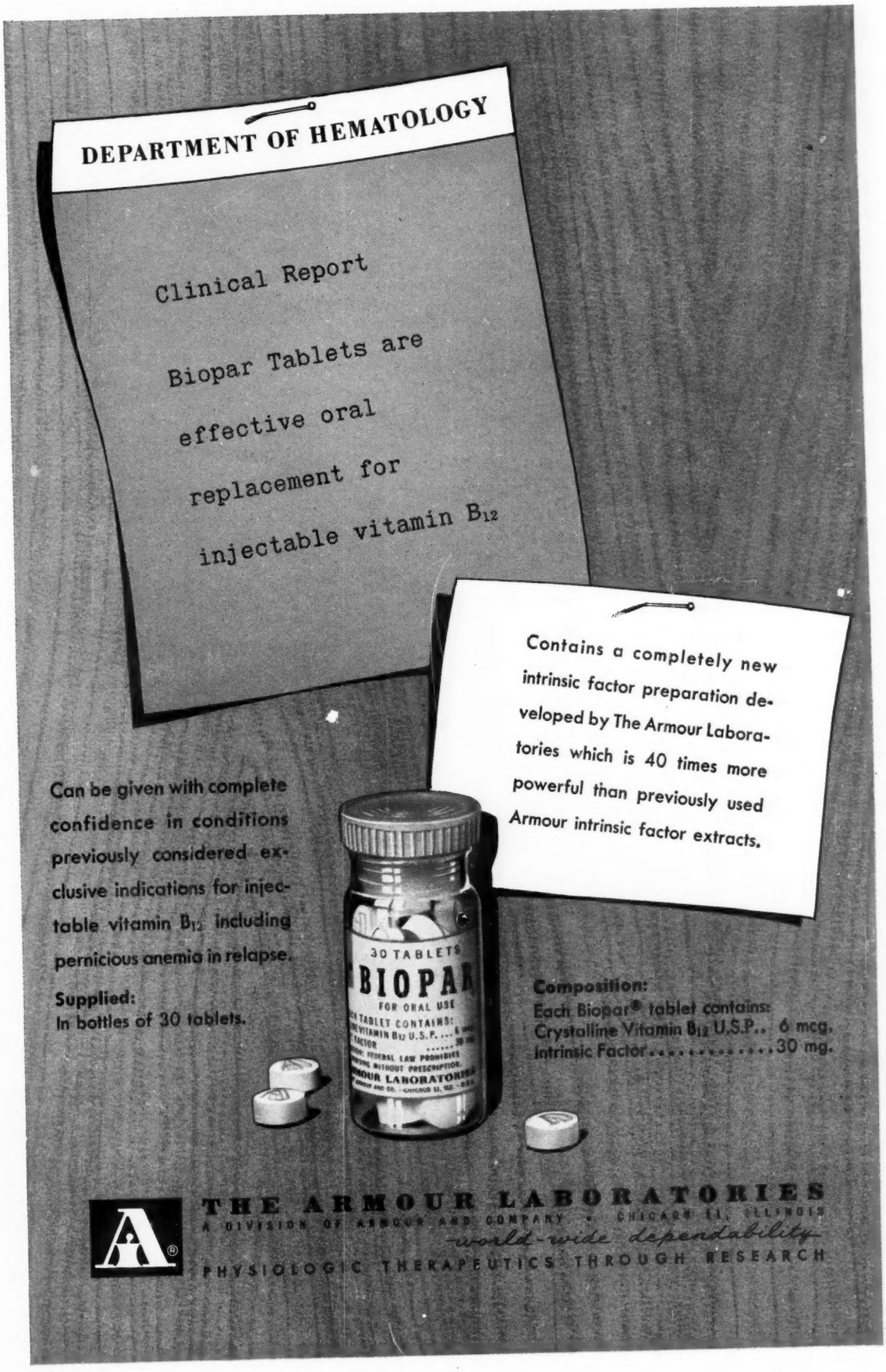
SUPPLIED:

10 cc. bottles containing 1.0 Gm. crystalline Terramycin amphoteric in raspberry-flavored, nonalcoholic vehicle with specially calibrated dropper.

Pfizer

world's largest producer of antibiotics

Antibiotic Division, **CHAS. PFIZER & CO., INC.**, Brooklyn 6, N. Y.


DEPARTMENT OF HEMATOLOGY
Clinical Report
Biopar Tablets are effective oral replacement for injectable vitamin B12
Contains a completely new intrinsic factor preparation developed by The Armour Laboratories which is 40 times more powerful than previously used Armour intrinsic factor extracts.
Can be given with complete confidence in conditions previously considered exclusive indications for injectable vitamin B12 including pernicious anemia in relapse.
Supplied:
In bottles of 30 tablets.
30 TABLETS
BIOPAR
FOR ORAL USE
Composition:
Each Biopar® tablet contains:
Crystalline Vitamin B12 U.S.P.. 6 mcg.
Intrinsic Factor.....30 mg.
THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY • CHICAGO 11, ILLINOIS
world-wide dependability
PHYSIOLOGIC THERAPEUTICS THROUGH RESEARCH

For that stubborn case of **CYSTITIS**

...especially in the presence of obstruction...an urologic antiseptic of choice...both bactericidal and bacteriostatic...**MANDELAMINE®**

Brand of methenamine mandelate

because of its virtual "lack of toxicity and effective antibacterial action,"— Carroll, G., and Allen, H. N.: J. Urol. 55:674 (June) 1946.

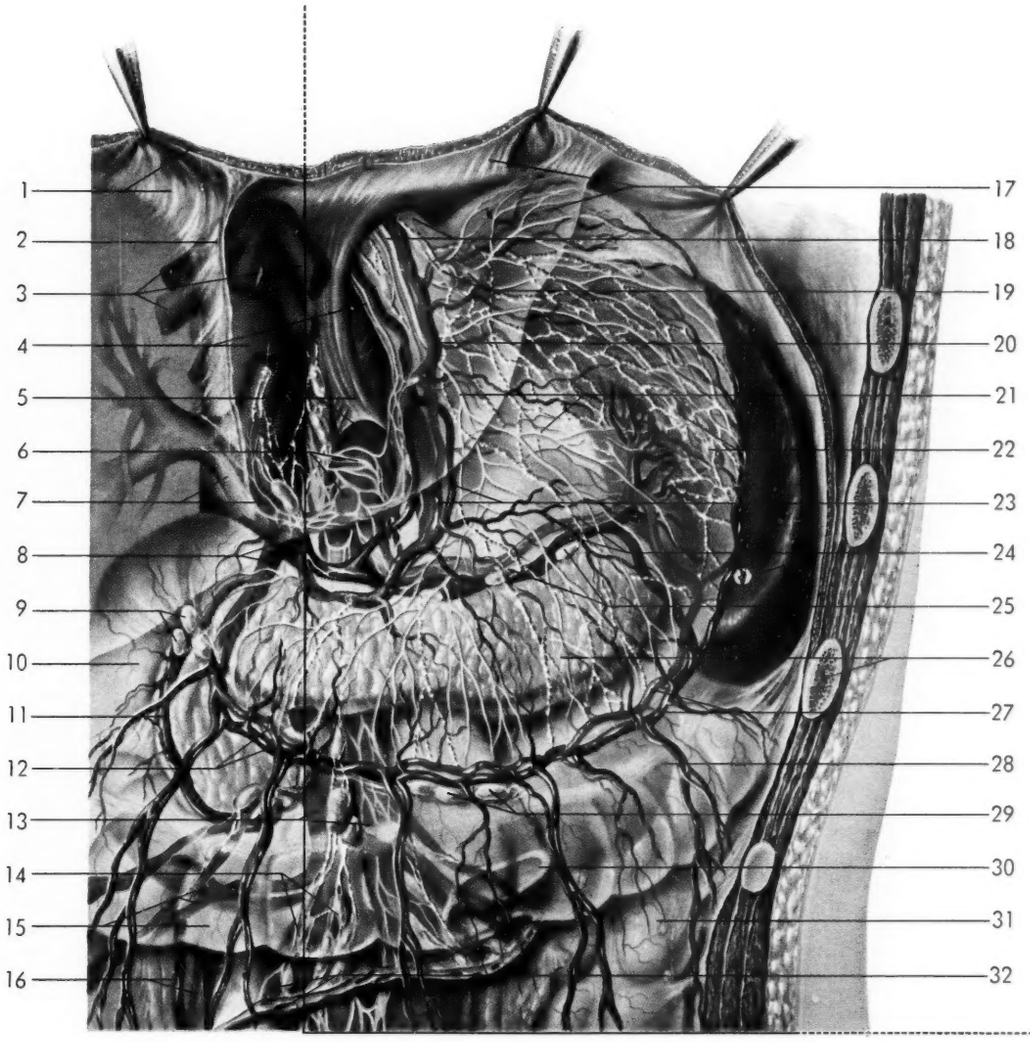
because it is "especially useful in long-standing infections in which permanent sterilization cannot be expected because an obstruction, stone or catheter cannot be eliminated."— Hinman, F., Jr.: California Med. (Jan.) 1952.

Recommended therapeutic dosage: 3 to 4 tablets t.i.d.

®Mandelamine is the registered trademark of Nepera Chemical Co., Inc., for its brand of methenamine mandelate.

NEPERA CHEMICAL CO., INC.
Pharmaceutical Manufacturers
Nepera Park, Yonkers 2, N. Y.

Upper Left Quadrant of the Abdomen



1 Diaphragm and coronary ligament
2 Falciform ligament
3 Hepatic veins
4 Inferior vena cava and right vagus nerve
5 Crus of diaphragm and abdominal aorta
6 Celiac artery and celiac plexus
7 Hepatic artery and portal vein
8 Gastroduodenal artery and vein
9 Subpyloric lymph nodes
10 Duodenum
11 Superior pancreaticoduodenal artery and vein
12 Right gastroepiploic artery and vein
13 Superior mesenteric artery and vein
14 Superior mesenteric lymph nodes
15 Transverse colon and right colic artery and vein
16 Spermatic artery and vein
17 Left triangular ligament and left lobe of liver
18 Esophagus and left vagus nerve
19 Paracardial lymph nodes
20 Esophageal branch of left gastric artery and vein
21 Gastric rami of vagus nerve
22 Splenic lymph nodes
23 Left gastric artery and coronary vein
24 Spleen and splenic artery and vein
25 Superior pancreatic lymph nodes
26 Pancreas and tenth rib
27 Left gastroepiploic artery and vein
28 Left kidney
29 Inferior gastric lymph nodes
30 Jejunum
31 Descending colon
32 Ileocolic artery and vein

This is one of a series of paintings for Lederle by Paul Peck, illustrating the anatomy of various organs and tissues of the body which are frequently attacked by infection, where aureomycin may prove useful.

Lederle

In peritonitis,
in intestinal infections,
and as a prophylactic adjunct
in surgery of the bowel—

Aureomycin

HYDROCHLORIDE CRYSTALLINE

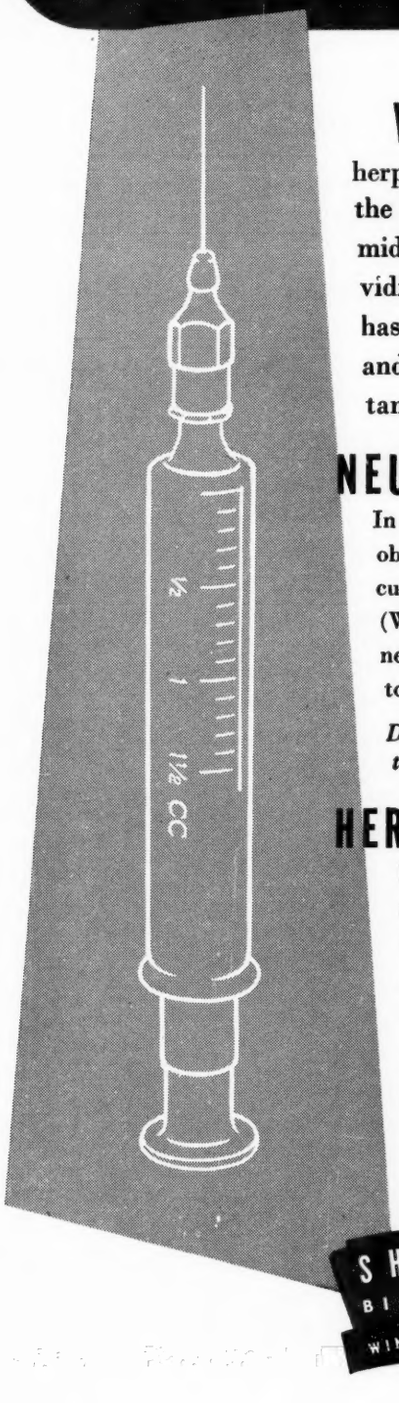
provides an unsurpassed
range of antimicrobial action

Literature available on request

LEDERLE LABORATORIES DIVISION
AMERICAN Cyanamid COMPANY
30 ROCKEFELLER PLAZA, NEW YORK 20, N. Y.

PROTAMIDE

FOR THE PATIENT SEEKING RELIEF FROM NERVE ROOT PAIN



WHEN the disturbing and painful symptoms of herpes zoster, or the stinging distress of neuritis brings the patient to you, quick relief is expected. Protamide helps solve this therapeutic problem by providing prompt and lasting relief in most cases. This has been established by published clinical studies, and on the valid test of patient-response to Protamide therapy in daily practice.

NEURITIS (Sciatic—Intercostal—Facial)

In a recent study* of 104 patients, complete relief was obtained in 80.7% with Protamide. 49 were discharged as cured after 5 days of therapy with no subsequent relapse. (Without Protamide, the usual course of the type of neuritis in this series has been found to be three weeks to over two months.)

Dosage: one 1.3 cc. ampul intramuscularly, daily for five to ten days.

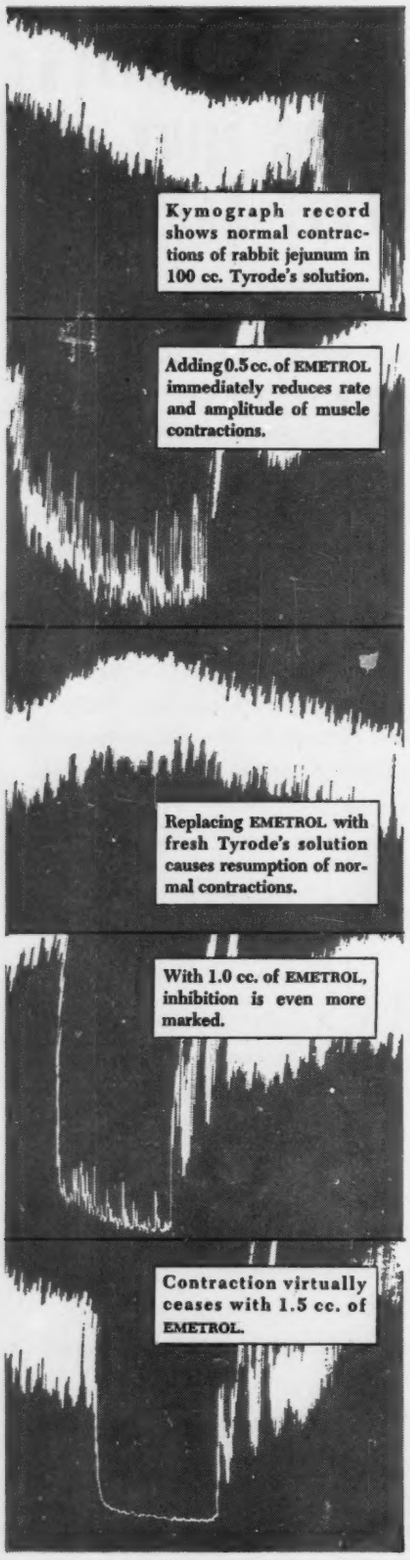
HERPES ZOSTER

A study* of fifty patients with Protamide therapy resulted in excellent or satisfactory response in 78%. (No patient who made a satisfactory recovery suffered from postherpetic neuralgia.) Thirty-one cases of herpes zoster were treated with Protamide in another study.* Good to excellent results were obtained in 28.

Dosage: one 1.3 cc. ampul intramuscularly, daily for one to four or more days.

* *A folio of reprints of these studies will be sent on request.*

SHERMAN LABORATORIES
BIOLOGICALS • PHARMACEUTICALS
WINDSOR DETROIT 15, MICH. LOS ANGELES


Kymograph record shows normal contractions of rabbit jejunum in 100 cc. Tyrode's solution.
Adding 0.5 cc. of EMETROL immediately reduces rate and amplitude of muscle contractions.
Replacing EMETROL with fresh Tyrode's solution causes resumption of normal contractions.
With 1.0 cc. of EMETROL, inhibition is even more marked.
Contraction virtually ceases with 1.5 cc. of EMETROL.

this is why

EMETROL®

controls epidemic vomiting physiologically

EMETROL (Phosphorated Carbohydrate Solution) permits effective physiologic control of functional nausea and vomiting—without recourse to drugs.

Thus EMETROL can be given *safely*—by teaspoonfuls to children, tablespoonfuls to adults—every 15 minutes until vomiting ceases.

IMPORTANT: EMETROL is always given *undiluted.* No fluids of any kind should be taken *for at least 15 minutes after taking* EMETROL.

INDICATIONS: Nausea and vomiting resulting from functional disturbances, acute infectious gastroenteritis or intestinal "flu," pregnancy, motion sickness, and administration of drugs or anesthesia.

SUPPLIED: Bottles of 3 fl.oz. and 16 fl.oz., at all pharmacies.

SAMPLES AND LITERATURE TO PHYSICIANS ON REQUEST

Kinney

KINNEY & COMPANY
COLUMBUS, INDIANA

1 *to escape pollens*

2 alternatives for the hay fever patient

2 *to relieve symptoms*

Pyribenzamine®

hydrochloride
(tripelennamine hydrochloride Ciba)

Once atop Pike's Peak, your hay fever patient can enjoy freedom from pollens. But for patients who must remain in a high-pollen environment, you can institute this effective therapy: one or two Pyribenzamine tablets, 3 or 4 times daily.

Alone and as an adjunct to desensitization, Pyribenzamine has proved effective in relieving hay fever symptoms, as evidenced by thousands of published case reports. On the basis of this evidence, no other antihistamine combines greater clinical benefit with greater freedom from side effects.

For your prescription needs, Pyribenzamine 50 mg. tablets are available in bottles of 100 and 1000 at all pharmacies.

Ciba *Ciba Pharmaceutical Products, Inc., Summit, N. J.*

2/1920M

Progressing Research Reveals

Nutritional and Metabolic Advantages from Oranges Eaten Whole

THAT the properly organized diet plays an essential role in health maintenance, today is universally accepted as a fundamental concept in nutrition. On this basis, oranges—properly peeled and eaten whole—merit a prominent place in the daily diet.

Orange juice is and remains probably the simplest palatable form in which to ingest the daily quota of vitamin C. *But of many other nutrients and physiologically valuable substances the fruit eaten whole supplies notably more than does the juice.*

Of the carotenes, for instance, the whole fruit provides six times as much as does the juice—1.0 mg. instead of 0.16 mg. per 100 Gm. of fresh weight.

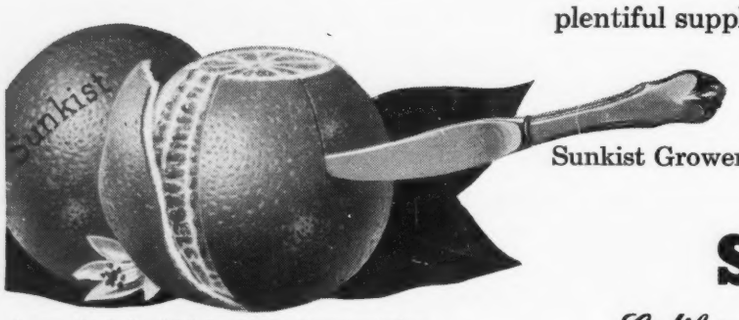
Of the protopectins, with their regulatory influence on intestinal function and improved absorption of certain noncaloric nutrients, the whole fruit contains ten times as much as does the juice—1.0 Gm. instead of 0.1 Gm. per 100 Gm.

Similarly with the bioflavonoids (which may well be concerned with capillary integrity), of these too the whole fruit contains ten times as much as does the juice—1.0 Gm. vs. 0.1 Gm.—and of inositol, one of the lipotropic B vitamins, it contains twice as much—0.4 Gm. as against 0.2 Gm. per 100 Gm. of fresh weight.

On the basis that the foods eaten should be chosen for their contribution to health maintenance, the suggestion "Eat an Orange a Day—and Eat It Whole" appears to be sound advice.

California Valencia Oranges are now in plentiful supply. Virtually everybody can benefit from their health-maintaining values.

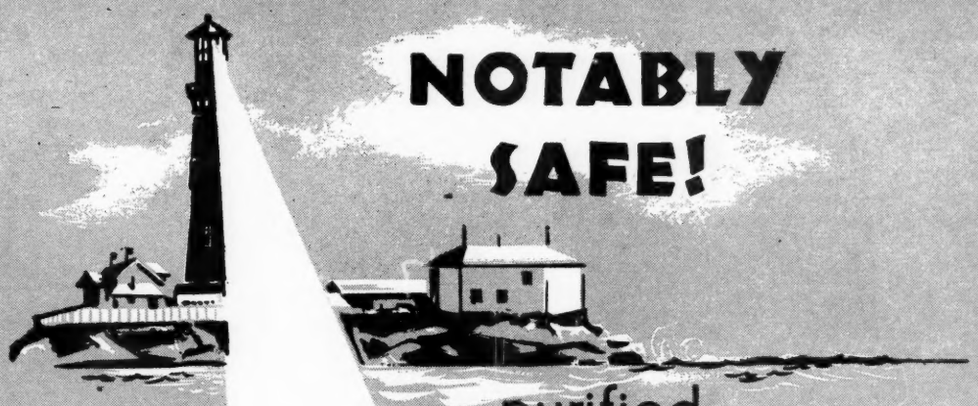
Sunkist Growers · Los Angeles 54, California



A practical, healthful source of protopectins

Sunkist®

California-Arizona Oranges



NOTABLY SAFE!

purified Corticotropin-gel wilson

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Purified Corticotropin-Gel Wilson is the **only** corticotropin-gel which has been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

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W

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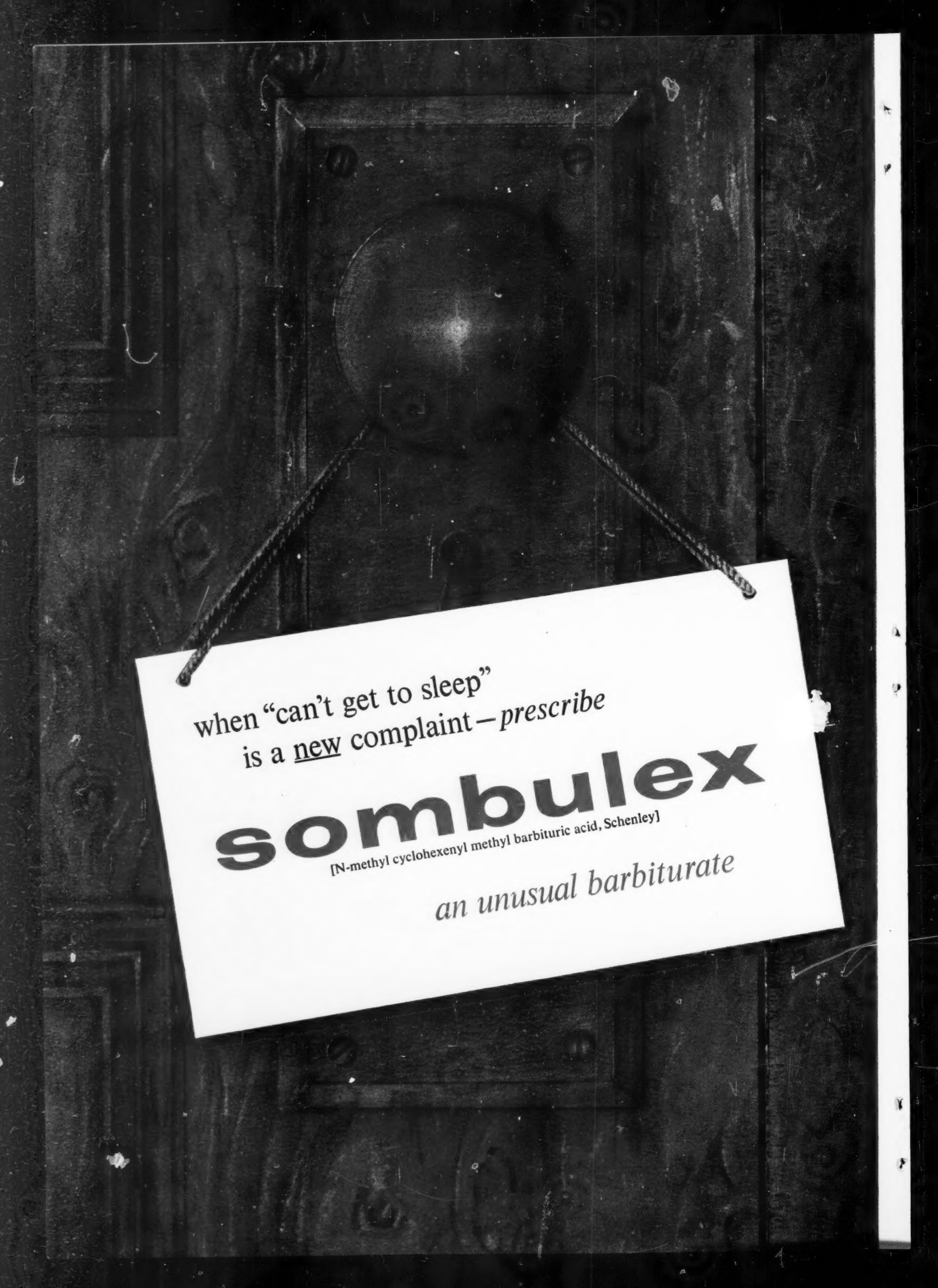
Detailed information about the use and dosage of Purified Corticotropin- Gel Wilson and Corticotropin Solution Wilson will be furnished on request.


when "can't get to sleep"
is a new complaint—prescribe
sombulex
[N-methyl cyclohexenyl methyl barbituric acid, Schenley]
an unusual barbiturate

sombulex* *is an unusual barbiturate*

because it works within 15 to 30 minutes and leaves the bloodstream within 3 to 4 hours, thus avoiding the danger of hangover for patients who do not need heavy barbiturate action.

When the stresses and strains begin to tell

...when the mind won't let the body rest, and patients complain for the first time..."Doctor, I can't get to sleep"... SOMBULEX is the prescription of choice for these first-time barbiturate patients. For them, 1 or 2 tablets taken with water or a warm beverage usually suffice to induce a night's refreshing sleep without hangover. Patients will not readily identify SOMBULEX as a barbiturate.

The unusual uses of **sombulex**

Because of its rapid yet nonpersistent action, 1 SOMBULEX Tablet will help restore *interrupted* sleep without subsequent hangover, or permit a relaxing cat nap before a busy evening. One SOMBULEX Tablet also will help the new night-shift worker adjust to a daytime sleeping schedule. NOTE: The action of SOMBULEX may be too short lived for the patient already dependent upon long-acting barbiturates. SOMBULEX is supplied in bottles of 100 tablets, each containing 0.26 Gm. (4 gr.) N-methyl cyclohexenyl methyl barbituric acid, *Schenley*.

SCHENLEY LABORATORIES, INC. schenley

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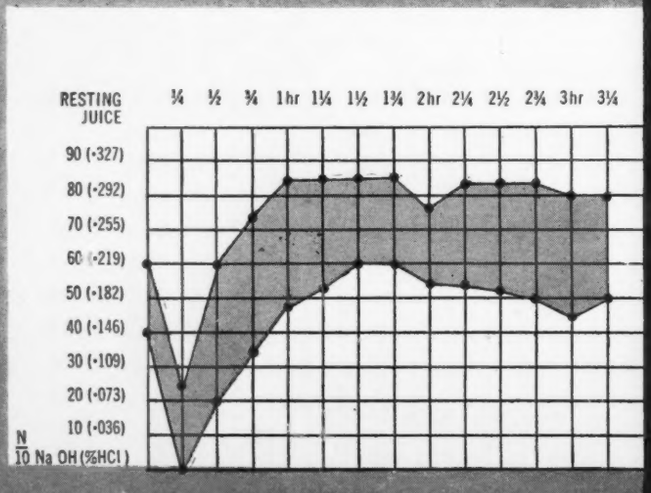
Nulacin

for maintained gastric anacidity

The Key to Successful Peptic Ulcer Therapy

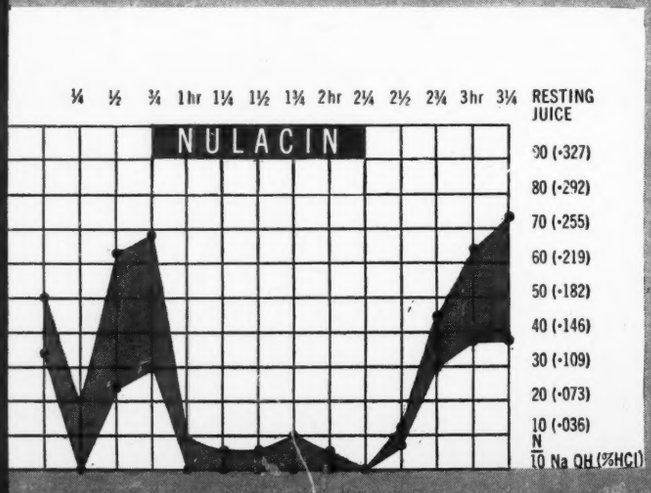
GASTRIC ANALYSIS. Superimposed gruel fractional test-meal curves of five patients with peptic ulcer.

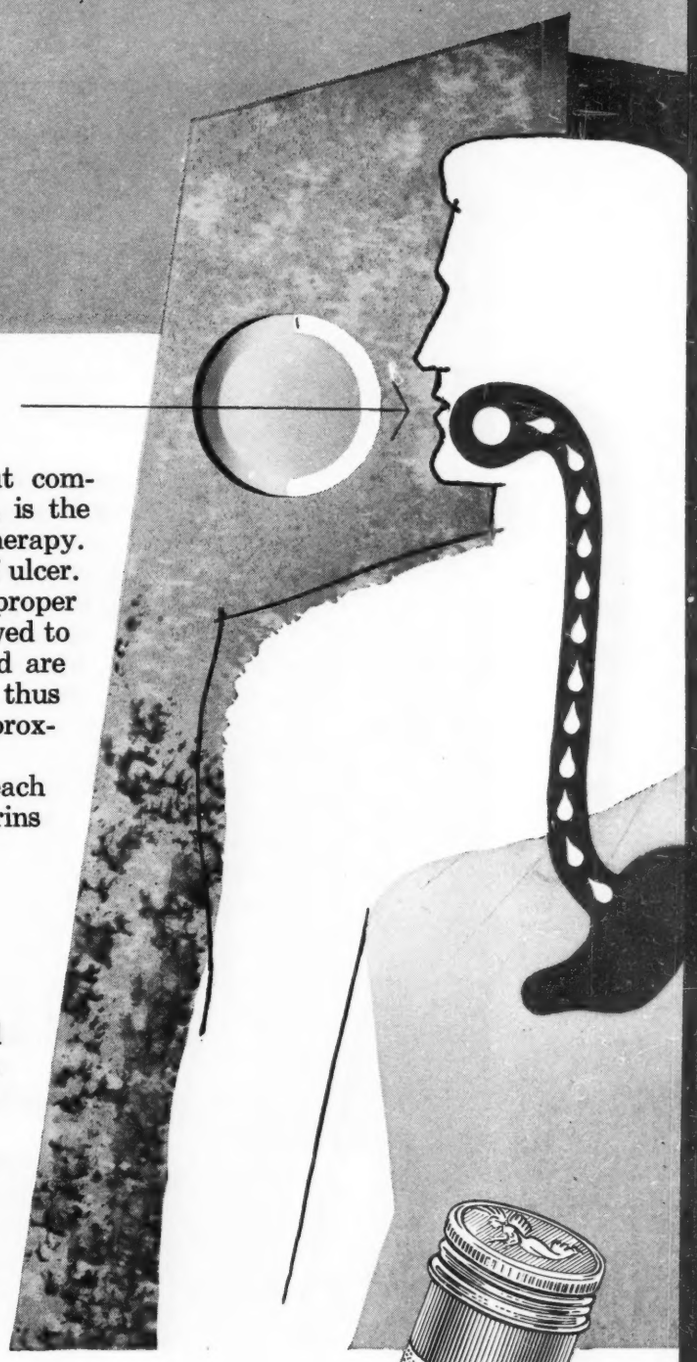
—— free HCl



GASTRIC ANALYSIS. Same patients, two days later, showing the profound and sustained neutralizing effect of sucking Nulacin tablets (three an hour).

—— free HCl





Continuous and complete acid neutralization, without complicated apparatus and while the patient is ambulant, is the outstanding contribution Nulacin makes in peptic ulcer therapy.

Nulacin represents a new concept in the treatment of ulcer. The Nulacin tablet, conveniently proportioned and of proper hardness, is placed between the cheek and gum and allowed to dissolve. Its antacid ingredients are slowly released and are carried to the stomach. Gastric hydrochloric acid is thus neutralized as it is elaborated, maintaining the pH at approximately 7.0. In this manner, healing is encouraged.

Highly palatable and providing only 11 calories, each Nulacin tablet is prepared from milk combined with dextrins and maltose and incorporates:

Magnesium trisilicate	3.5 gr.
Magnesium oxide	2.0 gr.
Calcium carbonate	2.0 gr.
Magnesium carbonate	0.5 gr.
Ol. Menth. pip.	q.s.

In this combination and because of the unique method of administration employed, the efficacy of the antacids in Nulacin is considerably greater than that of a similar quantity taken in the conventional manner.

For the treatment of active ulcer, the patient should be instructed to suck Nulacin tablets, two or three every hour, beginning one-half to one hour after each meal. The efficacy of the tablet is greatly reduced if it is chewed and swallowed.

Nulacin is available in tubes of 25 tablets at all pharmacies.

Horlicks Corporation

Pharmaceutical Division

RACINE, WISCONSIN

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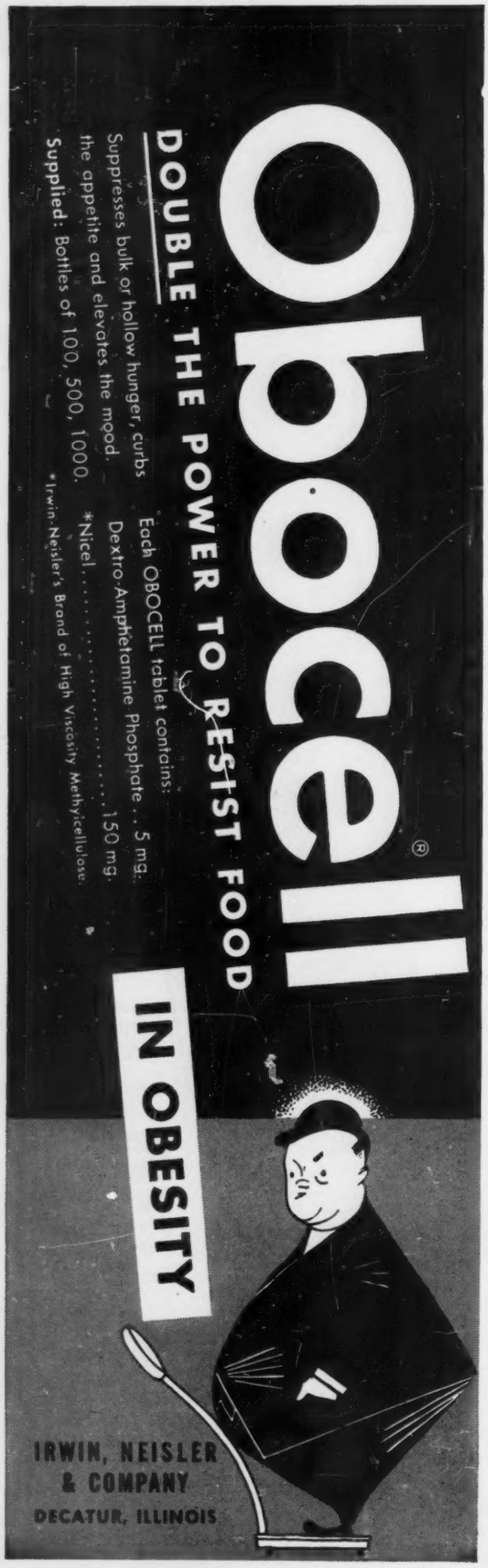
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Meat...

and the Therapeutic Value of Adequate Protein

Much evidence can be cited in favor of a high protein intake after surgery, trauma, infection, or burns. In supporting the many anabolic and defense mechanisms of the organism in physiologic stress,[1] high-quality protein—such as that of meat—assumes the status of an important therapeutic agent.[2]

Phagocytic activity,[3] formation of antibodies,[4] and rapid healing of wounds[5] are favorably affected by ample protein nutrition. Remission of peptic ulcer,[6] improved resistance to infectious disease,[4] and maintenance of plasma proteins after surgery[7] are other therapeutic effects attributed to an ample protein intake. In the management of ulcerative colitis, protein represents a primary need.[8] Recent advances in the treatment of extensive burns and of hepatic disease emphasize the value of high protein feedings.[9]

These experimental and clinical findings establish the therapeutic value of high protein intake.[10] To assure therapeutic protein adequacy, the dietary should provide a liberal margin of protein over normal requirements.

Meat is an important source of high-quality protein, containing essential as well as nonessential amino acids. In addition, it supplies significant amounts of B group vitamins and of iron, phosphorus, and other needed minerals.

REFERENCES

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1-139A

condition	*incidence of liver dysfunction*	*incidence of blood lipid abnormalities*	*suggested therapy*
obesity	frequent + + +	frequent + +	Methischol plus balanced low calorie diet.
diabetes	frequent + + + +	frequent + + +	Methischol as adjunct to diet. Insulin as necessary.
atherosclerosis	frequent + + +	frequent + + + +	Methischol and high protein, low fat diet.
coronary disease	frequent + + +	frequent + + + +	Methischol as adjunct to high protein, low fat diet and specific therapy.
alcoholism	frequent + + +	frequent + +	Methischol plus high protein diet.

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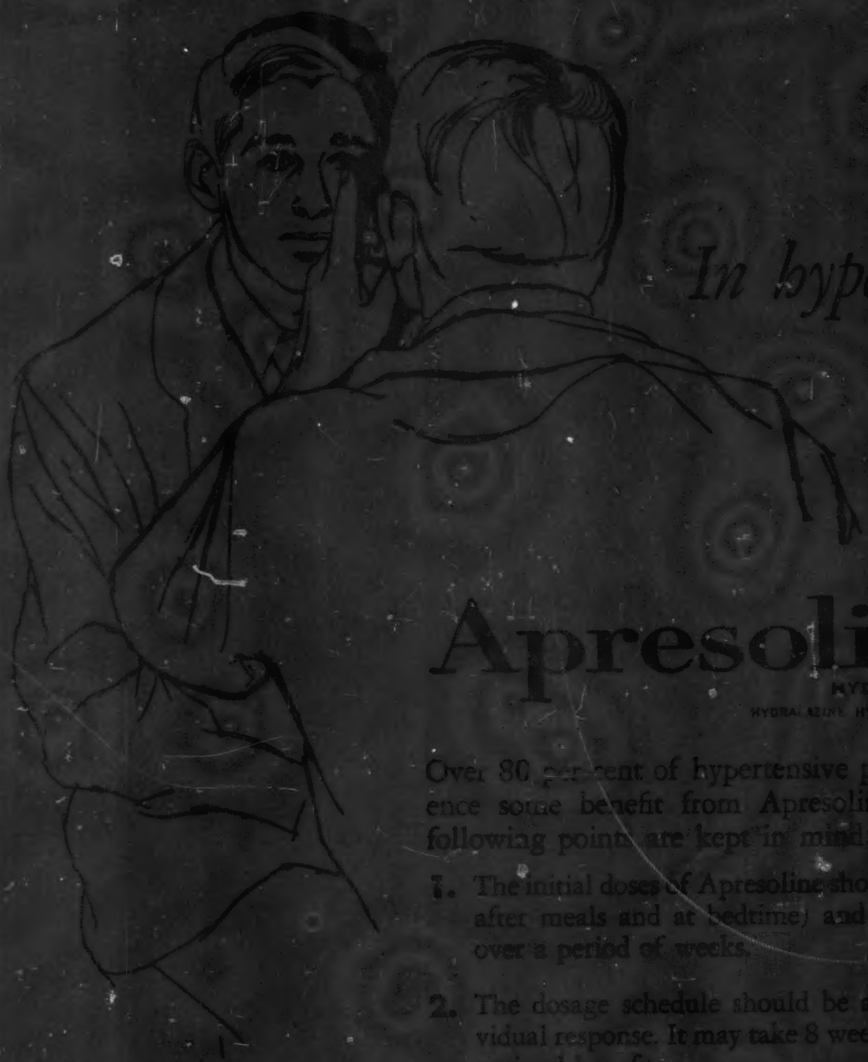

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